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PRODUCTION OF RETICULOCYTES, ERYTHROCYTES AND HEMOGLOBIN IN ANEMIA

THEIR RESPONSE TO CERTAIN TYPES OF THERAPY

WILLIAM P. MURPHY, M.D.

BOSTON

The magnitude of the rise in reticulocytes following the institution of therapy has been quite generally accepted as a means of evaluating the potency of various substances used in the treatment for pernicious anemia. The rate of the reticulocyte response and subsequent return to a normal level may also indicate the efficiency of the therapeutic substance used.

The magnitude of the response of the reticulocytes will depend to some extent on the method of staining and the technic employed in counting the cells, on the initial erythrocyte count at the time treatment is instituted, on the presence of complicating disease conditions and perhaps on the age of the patient. If these factors are given due consideration, the form and magnitude of the reticulocyte curve serve as a rough index of the potency of various substances used, particularly if treatment is carried out perorally in the usual manner and the amount of potent material used is limited by the patient's ability to ingest the liver substance.

With the introduction of highly concentrated and potent liver extract for parenteral administration, whereby large amounts of active material may readily be given, the magnitude of the reticulocyte response is not directly proportional to the amount of potent material used, nor is the accompanying increase in erythrocytes necessarily directly proportional to the rise in reticulocytes. Consequently, and because the primary object of treatment is to elevate the level of and improve the character of the erythrocytes, it would seem advisable to rely more on increases in the erythrocytes as a means for determining the actual comparative effectiveness of the various substances used.

Riddle and Sturgis [1] gave by stomach tube in a single initial dose large amounts of liver substance as liver extract. Following this treat-

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From the Medical Clinic of the Peter Bent Brigham Hospital.

Read before the Association of American Physicians, Washington, D. C., May 11, 1933.

This study was aided by a grant from the DeLamar Mobile Research Fund of Harvard University.

1. Riddle, M. C., and Sturgis, C. C.: Effect of Single Massive Doses of Liver Extract on Patients with Pernicious Anemia, Am. J. M. Sc. **180**:1 (July) 1930.

ment, the reticulocyte response occurred sooner than was customary with smaller initial amounts of material, and, although in some instances there was a maximal peak of response, this was not proportional to the large amount of material used. They concluded that, "the magnitude of the reticulocyte response does not appear to be influenced by the presence within the body of an excessive amount of the active liver principle, a certain maximum number of reticulocytes being possible in any case, the number being related to the original blood level."

Connery and Goldwater [2] observed responses of the reticulocytes of about equal magnitude in patients treated intramuscularly with varying amounts of a concentrated solution of liver extract. The magnitude of the response was perhaps slightly greater for the various doses used than would be expected from maximal amounts of liver substance perorally, although the difference was not great. However, the increase in erythrocytes was more rapid after the larger than after the smaller doses and was more rapid in either case than is generally observed during peroral treatment.

Strauss and Castle [3] have likewise compared the effect of various doses of a solution of liver extract administered intramuscularly. The observations recorded by them indicate that the use of such small doses as that derived from 20 Gm. of liver may initiate a reticulocyte response of the same rate and magnitude as that initiated by a dose derived from 100 Gm. of liver. Neither of the aforementioned amounts of material used, however, produced erythrocytes at the maximum rate possible for the parenteral method of treatment.

Morris, Schiff, Foulger, Rich and Sherman [4] have recently produced interesting reticulocyte responses by the intramuscular administration of concentrated gastric juice. The rate and magnitude of the increase in reticulocytes are essentially similar to those following parenteral liver therapy, but the increase is maintained for many days. In spite of the high and prolonged rise in reticulocytes, the increase in erythrocytes occurred at a minimal rate of speed.

Further evidence that the reticulocyte curve cannot be used as a quantitative measure of the effectiveness of liver substances of all degrees of potency is shown in charts 1 and 2.

Patients treated by three different methods have been selected for comparison in chart 1, so that the initial erythrocyte levels and the

2. Connery, J. E., and Goldwater, L. J.: Parenteral Use of Liver Extract in the Treatment of Pernicious Anemia, J. A. M. A. **98**:1060 (March 26) 1932.

3. Strauss, M. B., and Castle, W. B.: Parenteral Liver Therapy in the Treatment of Pernicious Anemia, J. A. M. A. **98**:1620 (May 7) 1932.

4. Morris, R. S.; Schiff, L.; Foulger, J. H.; Rich, M. L., and Sherman, J. E.: Treatment of Pernicious Anemia, J. A. M. A. **100**:171 (Jan. 21) 1933.

peaks of the reticulocyte responses are about the same in each case compared. The rate of the reticulocyte response varied, however, according to the type of treatment used, being most rapid following intramuscular injections. In spite of the fact that there is little difference in the magnitude of the reticulocyte responses, the increase in erythrocytes was definitely more rapid in the patient treated intramuscularly.

Ordinarily the reticulocyte response occurs more quickly with intramuscular than with peroral therapy. That this is not entirely respon-

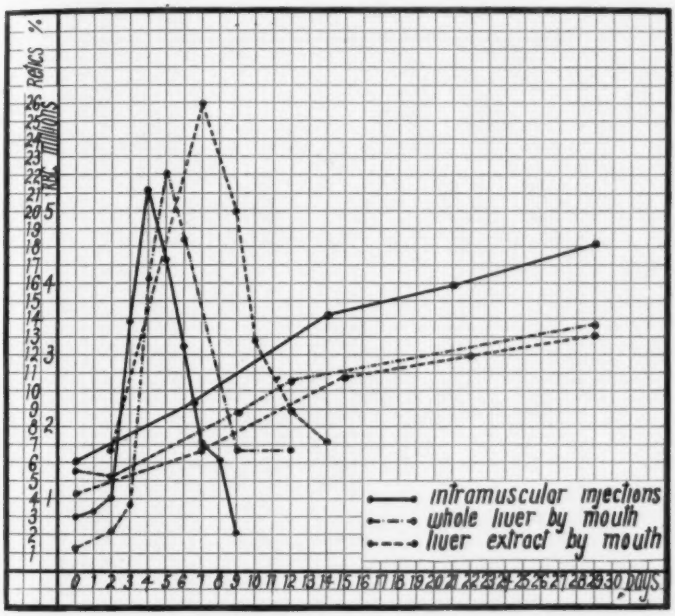

Chart 1.—A comparison of the rate of increases in erythrocytes in three patients who were treated by various means and in whom the initial concentration of erythrocytes and the magnitude of the increases in reticulocytes are comparable.

sible for the more striking increase in erythrocytes with the former method of treatment is illustrated in chart 2. An unusually slow response of the reticulocytes occurred following the intramuscular injection, but the erythrocyte response took place at about a maximum rate.

That the initial dose of concentrated solution given intramuscularly to one patient shown in each chart was actually far more potent than the amounts of liver or liver extract given to the other patients during the first few days of treatment is indicated by a comparison of the

amounts of liver from which the treatment of the various patients was derived. Each of the patients shown in the charts as having been treated intramuscularly received an initial injection of 6 cc. (derived from 200 Gm. of liver) of a concentrated solution of liver extract,[5] followed within twelve hours by a similar injection. After from seven to fourteen days each received 3 cc. (derived from 100 Gm. of liver) and a similar injection every seven days thereafter. The patients who received liver extract perorally received the amount derived from 300 Gm. of liver daily, and the other patient received 300 Gm. of liver prepared as the raw pulp daily.

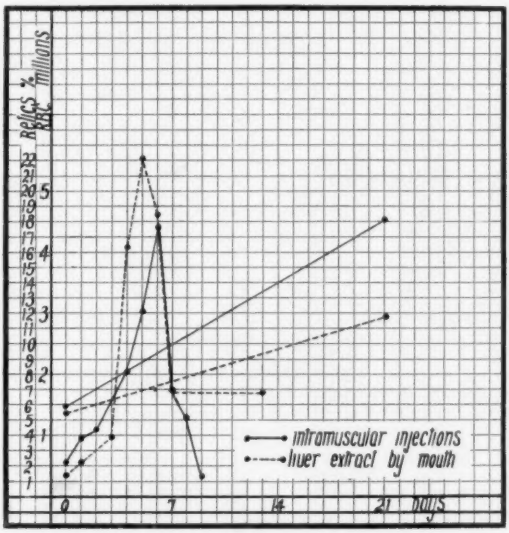

Chart 2.—A comparison of the rate of increases in erythrocytes in two patients as in chart 1 (see text).

Although in general the reticulocyte responses following the use of a concentrated liver extract intramuscularly are somewhat greater than those occurring with peroral treatment, the increases in erythrocytes are usually greater than might be anticipated from the height to which the reticulocytes rise. The increases in erythrocytes are also more constant and uniform than are the rises in reticulocytes. The average and the maximum and minimum peaks of the reticulocyte responses for various initial blood levels in forty-eight patients treated with the concentrated solution of liver extract after the manner previously described are

5. Solution liver extract-parenteral (N.N.R.) Lederle Laboratories, Inc.

shown in chart 3. The interval from the initiation of treatment to the peak of the rise has been rather constant; in four instances three days; in twenty-eight, four days; in nine, five days; in six, six days, and in one, seven days. The interval shows no definite variation dependent on the initial blood levels.

The magnitude of the increases in erythrocytes in this same group has been singularly uniform for those patients with comparable initial

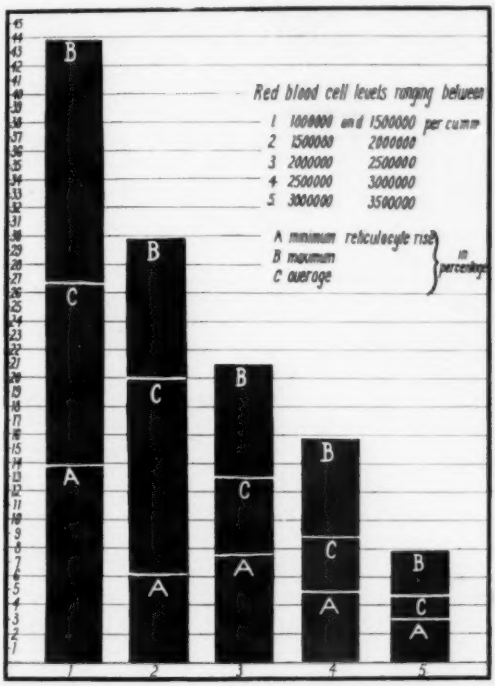

Chart 3.—The reticulocyte responses occurring at various initial red blood cell levels in patients treated with intramuscular injections of liver extract.

blood levels, and the gains have been distinctly more striking than those which have been observed previously with other forms of treatment. The average weekly and daily increases in the erythrocytes over various intervals and grouped according to the level when treatment was started are shown in the accompanying table. In order to compare these increases with those expected during peroral therapy, a curve showing the rate of increase observed in forty-two patients is presented in chart

4, together with a curve published by Minot and Murphy [6] in 1927, showing the improvement in ninety patients observed during treatment with whole liver. It is of interest to note that the former group attained an average erythrocyte level in six weeks equal to the average maximum level reached by the latter group during six months of treatment.

Minot [7] recently stated that if liver in amounts of 300 Gm. or liver extract No. 343 (N. N. R.) derived from 500 Gm. of liver is given daily (perorally), the concentration of red blood cells usually increases by about 2,500,000 cells (an average of 80,000 per day) in thirty days, when the concentration of the cells is less than 2,000,000 per cubic

Average Increases in the Number of Red Blood Cells Following Intramuscular Injections of Liver Extract

Initial Erythrocyte Levels		Interval,		
Ranging Between	Average per C.Mm.	Days	Average Increase	Average Increase per Day
1,000,000 and 1,500,000	1,230,000	7	840,000	120,000
		14	1,790,000	128,000
		21	2,410,000	114,000
		28	3,050,000	109,000
1,500,000 and 2,000,000	1,750,000	7	720,000	103,000
		14	1,370,000	98,000
		21	1,840,000	88,000
		28	2,370,000	85,000
2,000,000 and 2,500,000	2,260,000	7	620,000	89,000
		14	1,250,000	89,000
		21	1,450,000	69,000
		28	1,760,000	63,000
2,500,000 and 3,000,000	2,740,000	7	510,000	73,000
		14	1,050,000	75,000
		21	1,500,000	71,000
		28	1,820,000	65,000
3,000,000 and 3,500,000	3,340,000	7	380,000	54,000
		14	980,000	70,000
		21	1,120,000	53,000
		28	1,070,000	38,000

millimeter, "or about as fast as it is possible for these elements to be manufactured." The average increase in the concentration of red blood cells during a period of twenty-eight days in a consecutive series of twenty patients with an initial concentration of cells less than 2,000,000 per cubic millimeter treated by means of intramuscular injections,[5] as described previously in this paper, was 2,700,000 per cubic millimeter, or an average of about 100,000 cells per day. This increase is about 25 per cent more rapid than that occurring with optimal peroral treatment as described by Minot. Increases as great as from 3,400,000 to 3,800,000 cells in twenty-eight days, or from 120,000 to 135,000 per day, are frequent. Whether or not this is a maximum rate remains

6. Minot, G. R., and Murphy, W. P.: A Diet Rich in Liver in the Treatment of Pernicious Anemia, J. A. M. A. **89**:759 (Sept. 3) 1927.

7. Minot, G. R.: The Importance of the Treatment of Pernicious Anemia on a Quantitative Basis, J. A. M. A. **99**:1906 (Dec. 3) 1932.

to be seen. Evidence available now indicates that only a portion of the active substance in the liver extract is utilized immediately in producing these striking responses, and that a fairly large portion is stored to be used as needed. Further concentration of the liver extract or the development of some other substance in the future may initiate even more rapid increases.

Another illustration of the rate of action of the liver material used intramuscularly is given in chart 5. Although the rate of the formation of erythrocytes varies inversely with the initial blood level, as has been previously shown, the rate is such in each group that an erythro-

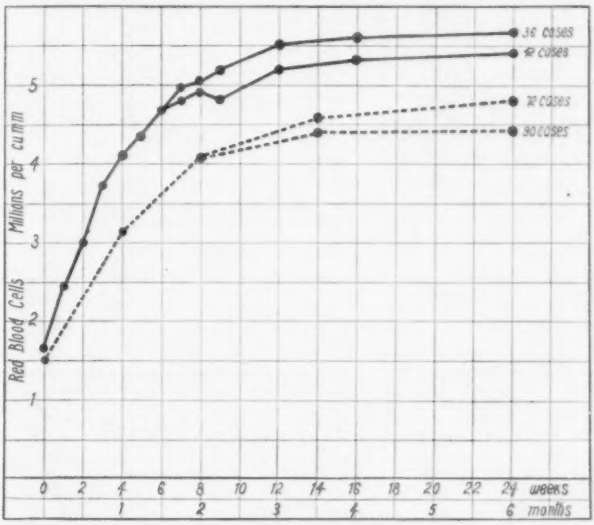

Chart 4.—A comparison of the average rate of improvement of the red cells in patients treated with whole liver and with intramuscular injections of liver extract. The dotted curve indicates the patients treated with whole liver (reproduced from Minot and Murphy [6]). The continuous curve represents the patients treated with intramuscular injections of liver extract. The lower line of each curve includes also those patients with complications or receiving inadequate treatment.

cyte level of between 4,000,000 and 4,500,000 cells per cubic millimeter is reached in twenty-eight days. From then on improvement takes place in each group at approximately the same rate.

The influence of iron therapy in addition to the injections of liver extract is well illustrated in chart 6. Improvement in the hemoglobin during the first few weeks occurs at essentially the same rate whether or not iron is given. At some time during the course of parenteral

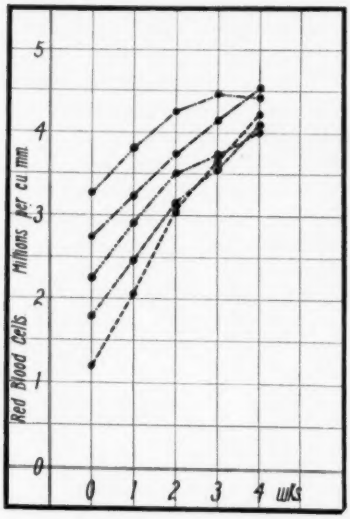

Chart 5.—Progress of the formation of red blood cells during one month of intramuscular treatment. The averages are grouped according to the initial blood levels.

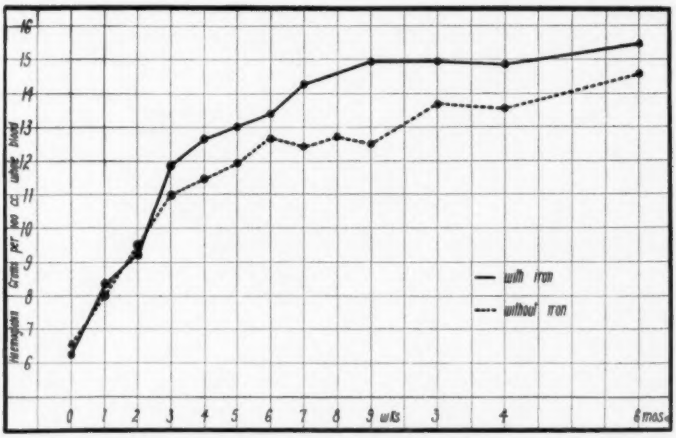

Chart 6.—A comparison of the average rate of improvement of the hemoglobin in patients with pernicious anemia treated with and without iron, together with intramuscular injections of liver extract.

treatment, usually within from three to five weeks after it is started, the use of iron gives an added stimulus to the increase in erythrocytes and hemoglobin. The definite lag in hemoglobin observed in those patients who did not receive iron, as shown in the lower curve of chart 6, will be seen to occur shortly before the time that there is a definite flattening in the upper curves of chart 4. This slowing up of the formation of erythrocytes owing to the developing deficiency in iron is, no doubt, more abrupt than might otherwise be expected.

COMMENT

It is well known that the magnitude, and to some extent the rate, of the response of the reticulocytes to therapy is in part dependent on the method of staining and technic of counting the reticulocytes, the number of erythrocytes present when treatment is started and the state of health of the patients in certain respects other than the anemia.

If the various secondary factors which influence the rise in reticulocytes are assumed to be constant, the magnitude of the response of the reticulocytes will indicate the potency of the material used if it is administered in submaximal amounts. The data presented, particularly for patients treated with maximal amounts of potent material, as with a concentrated solution of liver extract administered intramuscularly, indicate that a reticulocyte response of equal magnitude may be observed following the use of varying amounts of equally potent material, that the response will occur more quickly following the initial administration of large amounts, that the magnitude of the increase in erythrocytes may not vary directly with the magnitude and duration of the rise in reticulocytes and that the rate of increase of the erythrocytes is a more accurate indication of the effectiveness and potency of substances used in the treatment of patients with pernicious anemia than is the rate and magnitude of the reticulocyte response.

The explanation for the lack of correlation between increases in reticulocytes and erythrocytes as observed following treatment with various substances is not obvious and is probably not entirely controlled by the condition of the blood-forming organs at the time treatment is started. The variation in response to treatment by different means may be dependent on the rate of absorption or the utilization of the active principle under the various methods of its administration. If this is the case, it is probable that when administered in large amounts, as by intramuscular injection, the active material presented ready for the immediate use of the blood-forming organs causes more rapid maturation of the erythrocytes, so that the proportion of mature to immature cells (reticulocytes) in the circulation is greater than when less of the potent substance is available.

Is it possible, however, that two factors are present in the various materials used in the treatment for pernicious anemia, a stimulating (or reticulocyte-producing) and a maturing (or erythrocyte-producing) one? These may occur in varying proportions in different materials which have been used, the maturing occurring in greater proportion in the more refined and concentrated liver extract for intramuscular use.

In the treatment of the patient whose blood is in a state of relapse, it is desirable that improvement of this condition be promoted as rapidly as possible. Observations indicating an unusually rapid increase in erythrocytes following the intramuscular injection of initial large amounts of a concentrated solution of liver extract [5] (12 cc. prepared from 400 Gm. of liver) and followed by infrequent smaller injections are presented. That this material is of a high degree of potency and that treatment by this means insures optimal efficacy are well illustrated by the improvement shown.

The administration of large doses of iron during treatment with liver extract parenterally is strongly recommended. By this means one may be more certain to obtain the maximum effect of the liver material by preventing the development of deficiency in iron as a result of the rapid maturation of erythrocytes produced by the parenteral method of therapy.

MACROCYTIC ANEMIA IN DISEASE OF THE LIVER

JOHN VAN DUYN 2D, M.D.
SYRACUSE, N. Y.

The cause of the so-called pernicious blood picture is still one of the most interesting fields of study in modern medicine. It is now generally recognized that this type of anemia is merely one variety of faulty formation of blood and not a pathognomonic sign. Whatever disease process is able to bring about this particular disturbance in hematopoiesis may produce this blood picture.

The following introductory case first suggested to me that cirrhosis of the liver might be another such disease process. This case was presented at a medical clinic in the John Hopkins Hospital on March 8, 1931.[1]

A man, aged 50, showed a clinical picture of advanced hepatic cirrhosis together with signs strongly suggestive of pernicious anemia. The liver was markedly enlarged and nodular. The skin was moderately jaundiced (icteric index, 45). There were in addition glossitis, combined sclerosis and a macrocytic type of anemia. The hemoglobin was 70 per cent; the erythrocyte count, 3,000,000, and the color index, 1.15. These findings suggested complicating pernicious anemia. Against pernicious anemia, however, was the normal response of the gastric secretions to histamine. The free hydrochloric acid content was 48 cc. of tenth-normal sodium hydroxide; the total, 64. Necropsy, performed several months later, established the diagnosis as hepatic cirrhosis with "extensive scarring." The cord showed slight diffuse degenerative changes in the posterior columns. The bone marrow was hyperplastic.

This case is one of cirrhosis of the liver in which the blood developed a "pernicious" character; that is, the anemia was of the hyperchromic or macrocytic type as indicated by the high color index. Just why glossitis and combined sclerosis should have been present also cannot be discussed here.

The following questions are of first importance.

1. Is the macrocytic anemia secondary to, or independent of, the hepatic cirrhosis?

2. If it is secondary to the hepatic cirrhosis, can other diseases of the liver also cause this change in the blood?

From the Medical Service, Syracuse University Hospital.

Read at the Annual Meeting of the Alumni of Syracuse University Medical School, June, 1932.

1. This case is reported with the permission of Dr. Longcope.

3. If they can, might not the presence of a macrocytic anemia be taken, at times, as an indication of disease of the liver?

A few references from the literature will show that the occurrence of a macrocytic blood picture in cirrhosis of the liver has been widely recognized.

In 1913 Babonniex and Tixier [2] reported a case illustrating the "coexistence of cirrhosis and pernicious anemia." They cited two similar cases from the French literature and referred to several discussions on the subject. From these they stated that "it is difficult to draw any definite conclusions," but "all have the merit of attracting attention to the relationship of the cirrhotic to the anemia of the pernicious type."

Naegeli,[3] in his book on diseases of the blood published in 1912, merely included cirrhosis of the liver under the differential diagnosis of pernicious anemia. In a later edition, however, he was more specific,[4] stating that "certain hepatic cirrhoses show a high value of hemoglobin and a macrocytosis." Another comment is also significant: "The combination of pernicious anemia with cirrhosis of the liver is not at present clear to me. In one observation the cirrhosis was wholly in the foreground of all the symptoms and the pernicious anemia established later."

In Italy, Gamna made similar observations. In 1926 he [5] reported two cases of pigmentary cirrhosis of the liver in which there was a "tendency of the color index to increase to and above unity." He was impressed with the morphologic quality of the red cells, which showed "an anisomacrocytosis so marked as to call to mind the blood picture of pernicious anemia." In another paper [6] the degree of macrocytosis was reported: "In advanced atrophic cirrhosis there is found a more or less manifest tendency toward an increase in the size of the red cells, such that many of them, ranging from 20 to 25 per cent up to 40 to 45 per cent, surpass a diameter of 9 microns."

Again, in 1932, this interesting relationship was observed by Remen.[7] He reported an illustrative case and gave references to seven

2. Babonniex, L., and Tixier, L.: Sur un cas de cirrhose compliquée d'anémie pernicieuse, Gaz. méd. de Nantes **31**:61, 1913.

3. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 2, Leipzig, Veit & Co., 1912, pp. 434 and 429.

4. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923, pp. 321, 304, 320 and 350.

5. Gamna, C.: Contributo alla patologia ed alla clinica della cirrosi pigmentaria, Minerva med. **6**:797, 1926.

6. Gamna, C.: L'anisocitosi dei globuli rossi del sangue, Minerva med. **6**:730, 1926.

7. Remen, L.: Perniziöse Anämie und Leberzirrhose, Med. Klin. **28**:514 (April 8) 1932.

similar cases found largely in the German literature. The cirrhosis in Remen's case was considered secondary to the pernicious anemia. He added, however, that "cirrhosis of the liver, which at times is followed by a secondary anemia, may in exceptional instances be the cause of a pernicious anemia."

Perhaps the recent cases of Barker [8] and Cabot [9] are also examples of this syndrome. Both show apparently a macrocytic anemia in the presence of hepatic cirrhosis.

I have observed three cases in which disease of the liver was associated with anemia of the macrocytic type. The diameters of the red cells were measured in each case to confirm the macrocytosis and to determine its degree.

METHODS

In each case I determined the significant data on the blood, as indicated in the tables. For comparison, the earlier determinations in cases 1 and 3 are recorded from the case histories.

The hemoglobin was measured by the Sahli (Leitz) hemometer, which has a standard of 13.9 Gm. of hemoglobin equivalent to 100 per cent. The red blood cells were counted with a Levy-Hausser counting chamber and pipets. Capillary blood was used throughout.

The diameters of the red blood cells were measured with a Leitz filar micrometer ocular. The counting chamber was used in calibrating the length of the tube. The blood smears were stained with the Groat-Jenner stain. In measuring the diameters of the red cells, only the round cells were chosen, according to the method of Grosh and Stifel.[10] Measurements were made to 0.1 micron and the groupings arranged to correspond with those of Price-Jones.[11] The control curve was made from the blood of two normal healthy persons. In each instance 500 cells were measured.

The question of the serum bilirubin raising the hemoglobin value in patients showing jaundice was also considered. In two cases in which the icteric index was 100, the serum alone raised the hemoglobin less than 3 per cent. As none of the three cases to be reported showed an icteric index of over 100 at any time, this occasional small factor of error has been disregarded.

REPORT OF CASES

CASE 1.—*Diffuse Chronic and Acute Hepatitis (Pathologic Diagnosis).*

History.—A. I., a man, aged 30, was admitted to the hospital on April 21, 1931, complaining of swelling of the abdomen of four months' duration.

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8. Barker, L. F.: Cirrhosis of the Liver with Ascites, Splenomegaly, Secondary Anemia and Endocrinopathies in a Girl of Seventeen, M. Clin. North America **14**:99 (July) 1930.

9. Cabot, R. C.: A Cirrhosis Problem: Biliary Versus Laennec's, Case 17282, New England J. Med. **205**:107 (July 9) 1931.

10. Grosh, L. C., and Stifel, J. L.: The Diameter of the Red Blood Cells in the Differentiation of Anemias, Arch. Int. Med. **36**:874 (Dec.) 1925.

11. Price-Jones, C.: Diurnal Variation in the Sizes of Red Blood Cells, J. Path. & Bact. **23**:371 (Dec.) 1920.

For five years the patient had been working in a battery repair shop. His special duties, those of recharging batteries, required his almost continual presence in a closed room frequently cloudy with fumes. Although he had noticed an increase in infections of the upper respiratory tract, general weakness and occasional gastric upsets, he persisted at work until shortly before admission. For about four months the size of the abdomen had been gradually increasing. He had never been a heavy drinker.

Physical Examination.—When admitted the patient was not acutely ill, but suffered from abdominal distention. The skin was slightly jaundiced. Following the aspiration of a liter of ascitic fluid, the liver could be palpated a full handbreadth below the costal margin. Its surface was fairly smooth and somewhat tender; the edge was firm. The spleen was not palpated.

Course.—In spite of frequent aspirations followed by temporary relief, the course continued downhill. Anemia gradually developed, at first of the microcytic type, and later macrocytic. A moderate degree of jaundice appeared and persisted until

TABLE 1.—*Determinations of Blood in Case 1*

Date	Hemoglobin, per Cent	Red Cells per C.Mm.	Color Index	Number of Estimations	Icteric Index
April 25 to April 26	91	5,090,000	0.89	2	15
June 30 to July 28	82	4,730,000	0.86	5	50
August 3, operation					
August 6 to August 17	75	4,010,000	0.90	3	..
September 2 to September 12	75	3,420,000	1.10	2*	..
October 25, discharge					
December 28	90	4,440,000	1.01	1*	..

* My determinations.

shortly before discharge. Three months after admission an exploratory laparotomy was performed in order to establish the diagnosis. A small piece of liver was removed, and the gallbladder drained. On October 10, after a stormy convalescence of two months, the patient was discharged as improved. Ascites had not recurred after closure of the wound.

Clinical Diagnosis.—This diagnosis was hypertrophic biliary cirrhosis.

Laboratory Data.—Biopsy showed diffuse chronic and acute, periportal and pericentral hepatitis.

The ascitic fluid was a cloudy yellow; the specific gravity was 1.020. Inoculation into a guinea-pig gave negative results. During fasting the stomach contents showed free hydrochloric acid, amounting to 16 cc. of tenth-normal sodium hydroxide; total, 29. After an Ewald test meal there was no free hydrochloric acid, and the total amounted to but 19, owing probably to a regurgitation of duodenal contents. The patient refused further passage of the stomach tube. The Wassermann reaction of the blood was negative. The stained red cells showed slight anisocytosis and poikilocytosis, but no megaloblasts or normoblasts were found. On September 12 the mean diameter of the red cells was 7.92 microns.

CASE 2.—*Chronic Hepatitis or Hepatic Cirrhosis (Clinical Diagnoses).*

History.—T. M., a man, aged 52, of Irish descent, was admitted to the hospital on Dec. 9, 1931, complaining of nausea associated with painless jaundice. The jaundice had been noticed about a month, and the nausea, a few weeks before that.

The patient was a barber, but for the past thirty years he had been the proprietor of a small hotel. He admitted an almost continuous indulgence in alcoholic drinks. Nevertheless, his health had been good until about a month before admission, when he noticed increasing weakness, loss of weight, yellowness of the skin and frequent attacks of nausea without vomiting.

Physical Examination.—Besides deep jaundice, enlargement of the liver was the only significant finding. The firm edge of the liver could be palpated four finger-breadths below the costal margin. The surface was fairly smooth, but not tender. There was no demonstrable ascites or splenomegaly.

Course.—The patient remained in the hospital nearly six weeks, his temperature continuing normal throughout. One unsuccessful attempt at duodenal drainage was made. The jaundice cleared up gradually, but was still noticeable when the patient was discharged, on Jan. 19, 1932. Four months later the patient was again examined. The liver was found still greatly enlarged, though the jaundice had disappeared. Seven months after this a second check-up examination was made. The liver was considerably reduced in size, being palpable only within the costal angle.

TABLE 2.—*Determinations of the Blood in Case 2*

Date	Hemoglobin, per Cent	Red Cells per C.Mm.	Color Index	Number of Estimations	Icteric Index
Dec. 9, 1931, to Jan. 8, 1932.....	90	3,960,000	1.13	14*	80-100
January 19, discharge.....	..	.....	....	..	20
May 5	92	4,250,000	1.07	2*	5
December 1	94	4,940,000	0.95	2*	2

* My determinations.

Diagnosis.—At first the possibility of acute infectious jaundice was considered, but the subsequent course did not bear this out. The final diganosis rested between duodenitis with ascending infection of the biliary tract and beginning alcoholic cirrhosis.

Laboratory Data.—Following an Ewald test meal the gastric contents showed free hydrochloric acid, amounting to 34 cc. of tenth-normal sodium hydroxide; total, 52. The Wassermann reaction of the blood was negative. The stained red cells showed the same minor variations as in case 1. On December 10, the mean diameter of the red cells was 8.09 microns.

CASE 3.—*Hepatic Cirrhosis with Diffuse Hepatitis (Pathologic Diagnosis).*

History.—N. F., an English widow, aged 49, was admitted to the hospital on Nov. 9, 1931, complaining of intermittent diarrhea and general weakness of about one month's duration.

Following an attack of erysipelas three years before, a spastic gait developed, and the patient had much difficulty in walking. Since then there had been a gradually increasing generalized weakness, associated on admission with intermittent diarrhea.

Physical Examination.—The patient was very much underweight and extremely weak. At first she was unable to stand alone. The skin appeared somewhat pigmented over both extremities bilaterally. Marked chorioretinitis of uncertain origin was found. At the base of the left lung a few moist râles were heard.

When the patient was able to walk, she showed spastic paraplegia of the lower extremities. At that time examination of the abdomen revealed nothing unusual.

Course.—After an afebrile illness of five weeks' duration, the patient was discharged on December 19. Her condition was improved, but no diagnosis had been made. On April 4, 1932, between three and four months later, she was readmitted to the hospital, complaining of abdominal swelling of two weeks' duration. This time ascites was present, and there was in addition a moderate degree of jaundice (icteric index, 36). An exploratory laparotomy was performed. The patient died a few days later.

Necropsy Observations.—Besides the ascites and jaundice, the presence of a small, distorted liver was the only significant gross finding. Microscopic examination of the liver showed marked cirrhosis, probably of Laënnec's type, together with marked chronic and acute periportal hepatitis and areas of acute focal necrosis.

Laboratory Data.—On gastric analysis, the first specimen after the injection of histamine showed a free hydrochloric acid content of 37 cc. of tenth-normal sodium hydroxide, and a total of 49. The Wassermann reaction of the blood was negative. The stained red cells were no more unusual than in the other two cases. On April 27, the mean diameter of the red cells was 7.81 microns.

TABLE 3.—*Determinations of the Blood (Case 3)*

Date	Hemoglobin, per Cent	Red Cells, per C.Mm.	Color Index	Number of Estimations	Icteric Index
November 9 to December 14.....	78	4,350,000	0.87	5	..
April 27, 1932.....	81	3,860,000	1.05	2*	36

* My determination.

Although the color index of 1.05 in case 3 cannot be considered definitely above normal, the decrease in the red cells of nearly 500,000 per cubic millimeter, the hemoglobin remaining at essentially the same level, indicates clearly a macrocytic change in the blood.

SUMMARY OF CASES

The significant features in these three cases may be summed up as follows: In the first two, a definitely high color index was present during some period of the anemia; in the third, a macrocytic change in the red cells had taken place between admissions. In all three cases the stained red cells showed only slight anisocytosis and poikilocytosis. Free hydrochloric acid was demonstrated in the gastric contents of each patient. Disease of the liver was confirmed pathologically in cases 1 and 3, and was diagnosed clinically in case 2. Except in case 3, in which the possibilities of sprue and pellagra were eliminated at necropsy, there was no evidence to indicate the presence of any significant complication.

CURVES OF THE DIAMETER OF THE RED CELLS

The macrocytic character of the anemias is more clearly demonstrated by the accompanying chart. The curves represent graphically the diameters of the red cells, measured according to the method of Price-

Jones.[11] Curves of normal blood and of that in pernicious anemia are included for comparison.

The curve averaging the three cases of disease of the liver is seen to the right of the normal curves, and approaching that of pernicious anemia. It does not show the so-called spread characteristic of the curve of pernicious anemia, but demonstrates clearly the increased size of the red cells. The mean diameters correspond to the relative positions of the curves.

It may be added that individually, as well as taken together, the cases of disease of the liver show a mean diameter of the cells above

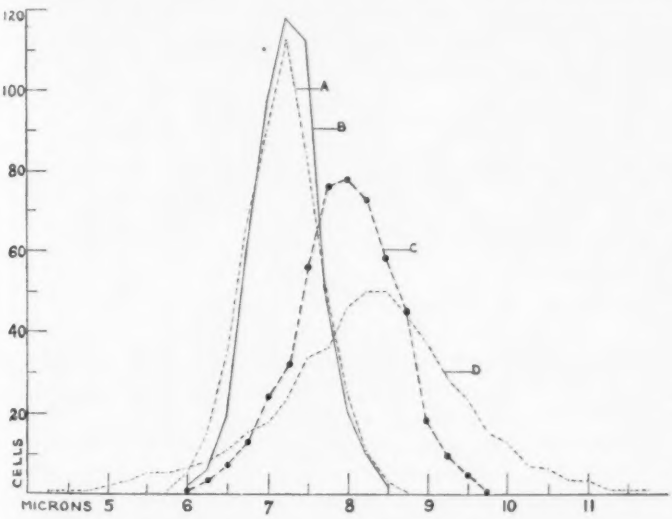

Chart showing the average curves of the diameters of the red cells in health, in disease of the liver and in pernicious anemia. *A*, Price-Jones' normal, averaging 100 curves (Price-Jones, C.: J. Path. & Bact. **32**:479 [July] 1929). *B*, my normal, averaging 2 curves. *C*, my cases of disease of the liver, averaging 3 curves. *D*, Price-Jones' cases of pernicious anemia, averaging 20 curves (Price-Jones, C.: J. Path. & Bact. **25**:487 [Oct.] 1922). The mean diameters are as follows: *A*, 7.20 microns; *B*, 7.26 microns; *C*, 7.94 microns, and *D*, 8.24 microns.

the estimated upper limit of normal determined as 7.72 microns by Price-Jones.[12]

These findings are additional evidence that the anemia associated with these cases of disease of the liver was of the macrocytic type.

12. Price-Jones, C.: Red Blood Cells in One Hundred Healthy Persons and in Pernicious Anemia, J. Path. & Bact. **32**:479 (July) 1929.

INCIDENCE OF MACROCYTIC ANEMIA IN HEPATIC CIRRHOSIS

To determine the incidence of macrocytic anemia in hepatic cirrhosis, the records of the hospital were consulted. Twenty-eight cases so diagnosed contained sufficient data for use. Of these twenty-eight, five, or 18 per cent, showed a high color index in the presence of anemia. For the five cases, the hemoglobin ranged between 33 and 87 per cent, averaging 65 per cent. The red cells numbered from 1,100,000 to 3,750,000 per cubic millimeter, averaging 2,470,000. The color index varied from 1.16 to 1.56, with an average of 1.35.

As control series, the cases of the patients with acute infectious jaundice and proved cholelithiasis admitted over the same period were reviewed. There were fourteen of the former and forty-five of the latter. None showed macrocytic anemia.

TABLE 4.—*Incidence of Macrocytic Anemia in Hepatic Cirrhosis, Acute Infectious Jaundice and Cholelithiasis*

	Number of Cases	Number Showing Macrocytic Anemia	Percentage
Hepatic cirrhosis	28	5	18
Acute infectious jaundice	14	0	0
Cholelithiasis	45	0	0

The figure of 18 per cent given in table 4 is probably somewhat high. Many of the cases of hepatic cirrhosis lacked laboratory data and could not be tabulated.

These findings suggest, however, that macrocytic anemia occurs not infrequently in hepatic cirrhosis, while it perhaps never occurs as secondary to acute infectious jaundice or uncomplicated cholelithiasis.

COMMENT

The anemias have been classified by Wintrobe [13] according to recent conceptions, depending on the difference in size and hemoglobin content of the red cell. He considers a macrocytic, a normocytic and two microcytic types. In the macrocytic type the cells are distinctly larger than normal, and the color index is uniformly high. This type is "notably represented by pernicious anemia in relapse," but may also be found occasionally in other conditions.

Just why macrocytic anemias develop at all is not yet clearly understood. The mechanism involved, however, has been partially brought

13. Musser, J. H., and Wintrobe, M. M.: Diseases of the Blood, in Tice, Frederick: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, 1920, vol. 6, pp. 753 and 843.

to light by Castle and his associates[14] in their studies of pernicious anemia. In considering this mechanism, the function of the liver will be seen to occupy an important position.

In 1929 Castle and Townsend[14a] showed that pernicious anemia is dependent on a deficiency in gastric secretion. This deficiency is almost invariably associated with, though not necessarily due to, achylia gastrica. According to Castle, the mucosa of the stomach normally secretes a substance, the "intrinsic factor," which acts on certain ingested proteins ("extrinsic factor") to form a principle which is active in regeneration of the blood ("effective principle"). If the secretion of the intrinsic factor is deficient, the active principle will not be formed, and pernicious anemia will result, at least hematologically. The feeding of liver supplies this principle preformed, and thereby causes the remission.

So much appears to be accepted. What becomes of the active principle under normal conditions and how it acts either normally or in pernicious anemia are still questions. Undoubtedly, it first passes through the portal vein to the liver, where it is taken up and to a large extent stored, the end-result of its presence in the body being normal hematopoiesis. The hematopoietic function is probably performed indirectly, either in building up Whipple's "parent pigment substances,"[15] in the possible production of some specific liver hormone,[16] or in regulating some phase of fat metabolism, such as the formation of cholesterol.[17]

Whatever the intricate steps may be, the function of the liver is undoubtedly concerned. In 1928 Schwarz[18] accepted some such function and explained the effect of the feeding of liver in pernicious anemia as equivalent to its restoration. He concluded that "only when this

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14. (*a*) Castle, W. B., and Townsend, W. C.: Observations on the Etiologic Relationship of Achylia Gastrica to Pernicious Anemia: II. The Effect of the Administration to Patients with Pernicious Anemia of Beef Muscle After Incubation with Normal Human Gastric Juice, Am. J. M. Sc. **178**:764 (Dec.) 1929; (*b*) Castle, W. B.; Townsend, W. C., and Heath, C. W.: III. The Nature of the Reaction Between Normal Human Gastric Juice and Beef Muscle, Leading to Clinical Improvement and Increased Blood Formation Similar to the Effect of Liver Feeding, ibid. **180**:305 (Sept.) 1930.

15. Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, Arch. Int. Med. **29**:711 (June) 1922.

16. Harris, S.: The Etiology of Pernicious Anemia: Is It Secondary to Hepatic Infection, Resulting in Deficiency of a Liver Endocrin? Tr. Am. Gastro-Enterol. A. **31**:208, 1928.

17. Muller, G. L.: The Relation of Cholesterol, Lecithin Phosphorus and Fatty Acids to the Remission of Pernicious Anemia, Am. J. M. Sc. **179**:316 (March) 1930.

18. Schwarz, E.: Megaloblastische Blutbildung und Leber, Wien. klin. Wchnschr. **41**:192 (Feb. 9) 1928.

definite but at present unknown function of the liver cells fails, do macrocytic and megaloblastic anemias develop."

It is now important to show that several conditions have been associated with macrocytic anemia, in which disease of the liver is an outstanding feature. Before considering these special conditions, however, the better known causes of the "pernicious blood picture" should first be reviewed. The latter seem to fall into two main groups.

The first group includes those which, according to Castle and his associates,[14b] are characterized by persistent symptoms of the gastro-intestinal tract. There is here a probable disturbance in either the formation or the absorption of the final effective principle. It consists in pernicious anemia, sprue, pellagra and some rarer intestinal disorders.

In the second group are the so-called chronic hemolytic anemias in which blood hemolysis is an assumed factor. Under this heading, Musser and Wintrobe[18] have placed hemolytic anemia of pregnancy, tapeworm anemia, hemolytic anemia of gastro-intestinal carcinoma and, possibly, certain anemias associated with tertiary congenital syphilis.

Rarely, the macrocytic blood picture may also occur in leukemia and malignant metastases to the bone marrow.[19]

Now may be considered the conditions in which disease of the liver is apparently an outstanding feature. These could be classified into a third distinct group. They include erythroblastosis foetalis, congenital syphilis, anemia infantum pseudoleukaemica, arseniuretted hydrogen gas poisoning, complicated disease of the gallbladder and cirrhosis of the liver. Each will be taken up separately to emphasize the association of macrocytic anemia with pathologic changes in the liver.

Erythroblastosis Foetalis.—This is a disease of early infancy, showing marked disturbances in the formation of blood. Naegeli[8] considered the blood picture as frequently simulating that of pernicious anemia. Recently, Diamond and his co-workers[20] have discussed the blood findings in twenty cases. They observed almost uniformly a marked macrocytic anemia. In each case the liver was greatly enlarged and showed "large numbers of islands of hematopoiesis scattered throughout the parenchyma."

Congenital Syphilis.—Although less frequently observed than in erythroblastosis foetalis, macrocytic anemia may be a prominent feature of congenital syphilis. The blood pictures may be indistinguishable.[20]

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19. Cornell, B. S.: The Etiology of Pernicious Anemia, Medicine **6**:375 (Sept.) 1927.

20. Diamond, L. K.; Blackfan, D. K., and Baty, J. F.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, J. Pediat. **1**:269 (Sept.) 1932.

Regarding the liver in congenital syphilis, according to MacCallum,[21] "perhaps the commonest change is a general retardation in its development, so that at birth it still appears as an organ actively engaged in blood formation."

Anemia Infantum Pseudoleukaemica.—This is a third disease of early infancy in which the anemia may also be macrocytic. Shilling [22] stated that the blood picture may be "at times rather pernicious, at other times distinctly leukemoid." Naegeli,[4] in considering anemias with a high color index and macrocytosis, included "severe forms of anemia in infancy, especially anemia infantum pseudoleukaemica." In the liver, in this condition, he found that "intra-acinous erythropoiesis is outspoken."

These three anemias of infancy might be considered together, since the parenchyma of the liver shows blood-forming islands in each. As this pathologic change suggests, the liver may have failed to assume its adult erythropoietic function, and, therefore, to have reverted to its embryologic one.

On the other hand, the following three conditions may be considered as showing impairment of this function subsequent to a normal state of activity.

Arseniuretted Hydrogen Gas Poisoning.—Dudley,[23] in 1919, reported thirty cases of poisoning due to the arsenic-contaminated gas evolved from batteries on a submarine. Of the thirty patients, twelve showed definite macrocytic anemia. All recovered without specific treatment. The symptoms were varied except in one respect—jaundice was uniformly present. Excessive destruction of blood cannot account for the jaundice in those cases in which there was no anemia. It was more probably of hepatic origin and due to toxic hepatitis.

Complicated Disease of the Gallbladder.—In 1924, Jones and Joyce [24] reported thirteen cases of disease of the gallbladder showing a blood picture resembling pernicious anemia. In five cases the anemia disappeared after cholecystectomy. These authors brought forth evidence "pointing to the presence of hemolyzing or other micro-organisms in the wall of the gall-bladder as being the possible cause of idiopathic progressive pernicious anemia." A study of the cases in this and a

21. MacCallum, W. G.: A Textbook of Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1932, p. 757.

22. Shilling, V.: The Blood Picture, St. Louis, C. V. Mosby Company, 1929.

23. Dudley, S. F.: Toxemic Anemia from Arseniuretted Hydrogen Gas in Submarines, J. Indust. Hyg. **1**:215 (Sept.) 1919.

24. Jones, N. W., and Joyce, T. M.: Infections of the Gall Bladder in Relation to Pernicious Anemia, Am. J. M. Sc. **168**:469 (Oct.) 1924.

subsequent report [25] suggests that in the cases in which the findings and course were not characteristic of true pernicious anemia, the macrocytic picture was due to disease of the liver. One patient in whom free hydrochloric acid was present in the gastric contents and whose blood returned to normal following cholecystectomy died six years later of "progressive obstructive biliary cirrhosis." In this case, as in others, an infection of the biliary tract resulting in hepatitis may well be assumed.

Hepatic Cirrhosis.—It has already been shown that macrocytic anemia occurs in cirrhosis of the liver. Disease of the liver is here, of course, understood.

There does exist, then, a distinct group of conditions which are associated with a macrocytic type of anemia and in which disease of the liver is apparently an outstanding feature. Assuming that the function of the liver plays a part in normal erythropoiesis, the pathologic changes in that organ might be held indirectly responsible for the development of the macrocytic blood picture. This answers in the affirmative the first two questions suggested by the introductory case.

The third question seems also to require an affirmative answer; that is, macrocytic anemia may, at times, be taken as an indication of disease of the liver. Subject to future confirmation, this offers a diagnostic sign which may be illustrated as follows: If a patient shows a macrocytic type of anemia in the presence of free hydrochloric acid in the gastric contents, disease of the liver should be suspected. With pernicious anemia thus essentially ruled out and the other aforementioned causes eliminated by further study, the diagnosis should be considered established. The exact pathologic changes present in the liver could not, of course, be foretold. It could be said only that the hypothetic erythropoietic function of the liver had been disturbed.

Although one could go no further than this, the sign might prove of great practical value in certain cases. For example, in the differential diagnosis of ascites, the hepatic origin would be established and an exploratory laparotomy avoided.

SUMMARY

1. An introductory case illustrating the occurrence of macrocytic anemia in cirrhosis of the liver is briefly reported.

2. References from the literature show this to be a widely recognized syndrome.

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25. Jones, N. W., and Joyce, T. M.: Further Remarks on Infections of the Gall Bladder in Relation to Chronic (Pernicious) Anemia, Am. J. M. Sc. **173**: 526 (April) 1927.

3. Three cases of disease of the liver are reported in which personal study has confirmed the macrocytic character of the anemia.

4. Twenty-eight cases of hepatic cirrhosis were reviewed from the records of the hospital. Macrocytic anemia was found in five cases, or 18 per cent.

5. The mechanism producing a macrocytic type of anemia is discussed. Disease of the liver is given a place in this mechanism.

6. A sign is suggested which may prove useful in the diagnosis of disease of the liver.

ALEUKEMIC MYELOSIS

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There are occasional cases of generalized myeloid hyperplasia and metaplasia which are not adequately described by the term myelogenous leukemia. Such cases are usually reported as aleukemic leukemia or aleukemic myelosis. In other groups of cases myeloid hyperplasia or metaplasia may be localized, forming single or multiple tumors within the bone marrow (multiple myeloma of the myeloid type) or extramedullary tumors (myeloblastomas). We wish to describe several instances of these less common forms of myeloid disease and to discuss their clinical recognition.

Table 1 presents the hematopoietic diseases appearing in the records of the University Hospital for a seventeen year period. The majority of the cases and all except one (case 3) of those reported in detail have been seen in the past eleven years and have been observed by one or by both of us. Necropsy and biopsy studies, for the most part, have been under the direction of Dr. G. H. Hansmann. Those cases in which the data were insufficient to establish a definite diagnosis have been excluded.

Secondary anemias have been excluded, as have the cases of idiopathic hypochromic anemia. Difficulty was encountered in the classification of a group of patients, mostly females, in whom there was an abnormal tendency to bleed, but in whom the attributes of hemorrhagic purpura and of hemophilia were lacking. These were excluded. One patient in whom erythroblasts consistently formed more than half of the nucleated elements in the circulating blood but in whom circulating myelocytes were also numerous has been classified as having leukemic myelosis. Permission for necropsy was not obtained, so that the possibility of erythroblastic anemia (leukemia) could not be excluded. We also studied a group of twelve children who suffered from a fatal hematopoietic disease which we have classified temporarily as subleukemic lymphatic leukemia. The children had low or normal total leukocyte counts without young cells, but with a severe neutropenia, laboratory and clinical evidence of purpura haemorrhagica, often some enlargement of the fixed lymphatic tissue and a progressive anemia

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with slight but definite evidence of regeneration and a color index of about unity. Infection, especially about the mouth, was prominent as a terminal event in most instances. Necropsy was obtained in three cases, biopsy of bone marrow in one and biopsy of a lymph node in still another. The lymph node appeared neoplastic (lymphoma), and the bone marrow showed cells of the lymphoid series to the exclusion of myeloid elements. The histologic evidence of leukemia in two of the cases that came to necropsy was not convincing in that "infiltration" of the parenchymatous organs was not marked. In the third case there was marked leukemic "infiltration" of the organs, especially the liver. From clinical and hematologic standpoints, the cases were all alike and resembled closely those reported by Abt [1] and by Hyland.[2]

TABLE 1.—*Hematopoietic Diseases at University Hospital Over Seventeen Year Period*

Condition	Cases	Condition	Cases
Pernicious anemia	492	Myelosis, leukemic (chloroma)	1
Anemia of pregnancy	4	Myelosis, aleukemic diffuse	4
Chlorosis	5	Myelomas, extramedullary	2
von Jaksch's anemia	3	Multiple myeloma, myeloid type	2
Aplastic anemia (benzene poisoning)	1	Multiple myeloma, plasma cell type	5
Aplastic anemia (neoarsphenamine)	1	Monocytic leukemia	3
Aplastic anemia, idiopathic	8	Lymphoma:	
Sickle cell anemia	1	Lymphocytic type, leukemic	86
Banti's syndrome	24	Lymphocytic type, subleukemic	12
Familial hemolytic icterus	14	Lymphocytic type, aleukemic	24
Acquired hemolytic icterus	4	Lymphoblastic type	36
Polycythemia vera	10	Endothelial type	6
Idiopathic neutropenia	4	Sclerosing type	76
Acute (blast cell) leukemia	13	Unclassified (biopsy not obtained)	36
Hematopoietic tumor (undifferentiated), extramedullary	2	Benign (?) lymphoma	1
Myelosis, leukemic	64	Purpura haemorrhagica, idiopathic	8
		Hemophilia	8

The following cases represent all of the instances of proved aleukemic myelosis and multiple myeloma (myeloid type) which we have recognized. Extramedullary myeloid tumors have also been included in this report.

REPORT OF CASES

CASE 1.—*Leukemic myelosis (aleukemic period induced by irradiation).*

A. D., a white man, aged 59, presented typical manifestations of leukemic myelosis. He was given repeated roentgen treatments over the spleen during a period of two years. A few of the blood counts are given to show the trend of the blood picture. This case is included to show an aleukemic interval such as may develop during irradiation in ordinary leukemic myelosis.

1. Abt, I. A.: A Case of Aleukemic Leukemia with Clinical Symptoms of Plastic Anemia, M. Clin. North America **8**:427 (Sept.) 1924.

2. Hyland, C. M.: Lymphatic Leukemia Without Leukocytosis, Am. J. Dis. Child. **39**:59 (Jan.) 1930.

TABLE 2.—*Blood Counts in Case 1*

Date	Hemoglobin	Erythrocytes	Leukocytes	Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
1/13/26	48	3,760,000	84,000	73	..	23	..	..	..	4	..	..	..	..	..	..
1/18/26	50	3,600,000	69,000	48	..	38	..	12	..	2	..	..	..	..	..	..
1/22/26	..	3,830,000	21,700	72	..	12	..	10	..	6	..	..	..	..	..	..
2/21/26	62	2,940,000	6,800	56	..	13	..	6	..	18	..	..	..	7	..	..
3/ 7/26	70	2,600,000	12,000	..	..	..	..	..	..	..	..	..	..	..	..	..
6/15/26	60	3,260,000	5,600	80	..	5	..	..	..	12	..	..	..	3	..	..
6/23/26	65	4,700,000	10,500	..	..	..	..	..	..	..	..	..	..	..	..	..
11/ 7/26	82	4,290,000	47,000	76	..	7	..	5	..	..	..	..	..	12	..	..
11/22/26	75	3,600,000	26,700	79	..	13	..	..	..	4	..	..	..	4	..	..
4/ 1/27	45	3,760,000	79,000	50	..	15	14	..	..	9	..	..	..	12	..	..
6/16/27	..	3,550,000	33,700	38	..	23	21	..	..	2	..	..	..	16	..	..
9/20/27	63	3,660,000	47,200	50	..	37	11	..	..	2	..	..	..	..	..	..
1/ 6/28	52	3,220,000	35,300	56	..	18	12	..	..	14	..	..	..	..	..	..
2/25/28	67	3,280,000	7,800	60	..	4	14	..	..	22	..	..	..	..	..	..

TABLE 3.—*Results of Examination of the Blood in Various Cases*

	Bleeding Time	Clot Retractility	Constrictor Test	Platelets, by Volume	Fragility Test	Prothrombin Time	Coagulation Time	Reticulocytes
Average normal	Less than 2 min.	4 + in 4 hrs.	Neg.	0.4 to 0.6 cc. per 100 cc.	Began at 0.44; complete at 0.36	Less than 10 min.	Less than 5 min.	Less than 1 per cent
Case 1	2 min.	4 + in 4 hrs.	Neg.	170,000 per cu.mm.	Began at 0.46; complete at 0.30	Normal	8½ min.	
Case 2	2 min.	1 + in 4 hrs.	Pos.	0.1 cc. per 100 cc.	Began at 0.50; complete at 0.36	Normal	3 min.	
Case 4	22 min.	None in 4 hrs.	Pos.	0.01 cc. per 100 cc.	Began at 0.44; complete at 0.36	Normal	5 min.	3.4 to 7.8 per cent
Case 5	15 min.	Poor in 4 hrs.	Pos.	0.1 cc. per 100 cc.	Began at 0.50; complete at 0.40	Normal	5 min.	10 per cent
Case 6	10 min.	None in 4 hrs.	Pos.	0.05 cc. per 100 cc.	Began at 0.44; complete at 0.34	Normal	4 min.	1.2 per cent
Case 7	2½ min.	4 + in 4 hrs.	Neg.	0.3 cc. per 100 cc.	Began at 0.46; complete at 0.38	Normal	5 min.	
Case 8	1½ min.	None in 4 hrs.	Neg.	1.2 cc. per 100 cc.	Began at 0.50; complete at 0.30	Normal	4 min.	2.4 per cent
Case 9	3 min.	Normal	Pos.	0.31 cc. per 100 cc.	Began at 0.46; complete at 0.44	Normal	3 min.	

CASE 2.—*Leukemic myelosis (spontaneous aleukemic period).*

H. L., a white man, aged 45, was admitted to the University Hospital because of a deep ulceration on the inner surface of the right cheek and enlarged lymph nodes at the angles of the jaw. The other superficial lymph nodes were not remarkable. The liver and spleen were moderately enlarged.

During the course of the disease his temperature was elevated continuously, frequently reaching 103 F. On Aug. 29, 1930, he received a small dose of roentgen rays over the right cheek (140 kilovolts, 5 milliamperes, 50 cm. skin target distance with a filtration of 0.25 mm. copper, and 1 mm. aluminum for fifteen minutes, which gave approximately 120 roentgens). There was temporary subsidence of the swelling. Exophthalmos of the right eye developed later, and the necrotic lesion in the mouth increased in size. The course was progressively downward, and death occurred on October 8.

TABLE 4.—*Blood Counts in Case 2*

Date	Hemoglobin	Erythrocytes	Leukocytes	Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/17/30	68	3,120,000	129,000	14	..	70	6	..	..	10	..	..	..	..	..	..
8/18/30	..	.....	112,000	20	14	56	..	..	..	3	..	..	..	..	7	..
8/25/30	59	3,330,000	53,000	..	..	..	..	..	..	..	..	..	..	..	..	..
8/29/30	..	.....	64,000	..	..	..	..	..	..	..	..	..	..	..	..	..
8/31/30	..	2,550,000	61,500	..	..	..	..	..	..	..	..	..	..	..	..	..
9/ 2/30	60	2,600,000	.....	84	..	4	..	..	..	12	..	..	..	..	..	..
9/ 7/30	60	2,550,000	60,100	..	..	..	..	..	..	..	..	..	..	..	..	..
9/11/30	..	.....	.....	78	1	1	..	..	7	9	..	1	..	3	..	..
9/12/30	..	.....	.....	80	..	..	..	..	..	19	..	..	..	..	1	..
9/14/30	..	.....	8,200	..	..	..	..	..	..	..	..	..	..	..	..	..
9/17/30	..	.....	7,100	76	..	..	..	..	..	18	..	5	..	1	..	..
9/19/30	35	1,580,000	6,300	76	..	..	..	..	1	18	..	4	..	..	1	..
9/29/30	32	1,460,000	9,300	32	8	18	19	..	..	22	..	1	..	..	..	..
10/ 1/30	40	1,860,000	15,500	16	2	34	39	..	..	5	..	..	..	4	..	..
10/ 3/30	..	.....	21,700	13	7	74	3	..	1	2	..	..	..	..	..	..
10/ 5/30	..	.....	21,300	11	7	35	35	..	1	9	..	..	..	2	..	..
10/ 7/30	30	1,560,000	34,000	..	..	..	..	..	..	..	..	..	..	..	..	..
10/18/30	..	.....	57,000	..	..	63	19	..	..	18	..	..	..	..	..	..

The results of various examinations of the blood are tabulated in table 3. On August 21 the basal metabolic rate was 31 per cent above normal, while on October 3 it was 26 per cent above normal.

It is to be noted that there was a spontaneous remission with a normal white cell count and an absence of immature cells. The polymorphonuclear leukocytes at this time showed more than the normal number of lobulations in their nuclei, i. e., an actual shift to the right. If infection caused the remission, it is peculiar that there should have been a shift to the right.

Necropsy disclosed diffuse myeloid hyperplasia and metaplasia.

CASE 3.—*Aleukemic myelosis, diffuse type.*

F. W., a white man, aged 53, came to the hospital because of weakness of six weeks' duration and edema which had been present for two weeks. The edema first appeared about the eyes, but later became generalized and was followed by some shortness of breath. The heart and lungs were essentially normal. The urine was scanty, varied from 1.016 to 1.020 in specific gravity and contained a few casts and, on one occasion, a trace of albumin. The nonprotein nitrogen of the blood was normal. The formed elements of the blood were not remarkable

(table 5). The patient's condition improved, and he left the hospital after seven weeks. However, he returned six weeks after discharge with the original complaints. At this time the edema was limited to the eyelids, and there was a slight icteric tint to the skin. There were signs of fluid in both pleural cavities. The blood pressure was 108 systolic and 78 diastolic, and the heart was normal. The liver was enlarged, but the spleen was not palpable on admission. The spleen gradually increased in size and for a few days was tender. Gastric analysis revealed an achlorhydria. The blood platelets numbered 355,000 per cubic millimeter. Petechiae and ecchymotic areas appeared, and the edema and dyspnea increased in severity. The patient died in coma ten days after admission. A hemolytic streptococcus grew in a blood culture drawn the day before death.

At necropsy there were many hemorrhages into and beneath the skin, the periosteum of the ribs, the epicardium and the capsules of the kidneys. The spleen was friable and bluish red, weighed 1,830 Gm. and contained numerous infarcts. There were grayish tumors along the coronary arteries and in the kidneys. The liver was enlarged, and the lymph nodes were congested. Bone marrow taken from the midportion of the femur was hyperplastic.

TABLE 5.—*Blood Counts in Case 3*

Date	Hemoglobin	Erythrocytes	Leukocytes	Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/26/19	96	5,070,000	5,320	69	..	..	..	1	..	28	..	2	..	..	..	..
9/23/19	..	.....	3,800	68	..	..	..	..	..	29	..	3	..	..	..	..
10/ 3/19	70	4,560,000	4,300	71	..	..	..	..	2	22	..	5	..	..	..	..
12/ 1/19	65	3,900,000	5,000	70	..	..	..	..	2	20	..	8	..	..	..	..
12/ 9/19	70	4,400,000	5,400	62	..	1	..	..	1	28	..	3	..	4	..	1
12/10/19	75	4,000,000	9,800	61	..	..	..	1	..	27	..	2	..	4	..	5

Microscopic examination showed infiltration or metaplasia in all organs, the predominant cell being of the myelocytic series. The tumors which could be seen grossly were composed of the same cells. Practically all of the splenic pulp was replaced by rapidly growing tumor tissue showing small areas of hemorrhage. In the liver the central veins, sinusoids and periportal spaces were distended with myeloid cells. There were many hemorrhagic areas in the kidneys as well as extensive collections of myeloid cells within the capillaries. These cells were also found distending the capillaries of all the tissues. The bone marrow was overgrown by myeloid cells.

CASE 4.—*Aleukemic myelosis, diffuse type.*

O. J., a white woman, aged 29, was admitted to the hospital on Sept. 29, 1929, because of profuse vaginal hemorrhage. She had noted increasing pallor and weakness during the preceding month and had had a moderately severe hemorrhage following the extraction of a tooth three weeks before admission. Subsequent to the extraction, the gums became swollen and tender. On admission the skin and mucous membranes were very pale, and although there were ecchymotic areas over the body the hemorrhage from the oral mucous membranes had ceased. The gums were so swollen as to cover entirely some of the teeth. The submaxillary lymph nodes were enlarged, but there was no lymphadenopathy elsewhere nor was the spleen or liver enlarged. Both breasts were enlarged and firm but not nodular or

tender. There was profuse uterine bleeding but otherwise the pelvic organs were normal. By weight of vaginal pads it was found that the loss of blood for twenty-four hours gradually decreased from 500 to 50 Gm. over a period of ten days during which time repeated transfusions were given. Irradiation of the gums caused a rapid subsidence of the swelling. The patient was discharged, but after two weeks at home she returned with markedly swollen gums, numbness of the lower lip and large, irregular, firm nodules in both breasts. A mass developed in the right side of the pelvis and extended upward to the level of the umbilicus, the spleen became palpable, and pain over the bones became prominent. Hemorrhagic neuroretinitis, ecchymotic areas in the skin and profuse uterine hemorrhage developed, and death occurred about four months after the first symptoms had appeared.

Laboratory studies showed normal urine and a negative Wassermann reaction. The basal metabolic rate was 1.4 per cent below normal on October 30, and on November 21 it was 23 per cent above normal. Roentgenograms of the bones were normal except for a defect in the mandible. The blood count was typical of

Fig. 1 (case 4).—Swollen infiltrated gums.

hemorrhagic purpura, as shown in table 3. There was no bilirubinemia. On October 3, the hematocrit reading was 14 per cent, and by the Newcomer method the hemoglobin was 5.3 Gm. Reticulocytes made up 4.8 per cent of the erythrocytes, and polychromatophilia and poikilocytosis were prominent. A clinical diagnosis of aleukemic myelosis was confirmed by a biopsy specimen from the gum.

Some of the neutrophils contained vacuoles, and the granules varied in size and tinctorial properties. The unclassified cells contained a bland, irregular nucleus of a purple tint, and their cytoplasm was pale blue and without granules with Wright's stain. They appeared to be of lymphocytic origin. No typical myelocytes were encountered in the smears, but different observers varied in their ideas as to classification. Two hematologists from other institutions looked at the blood smears. One reported toxic changes in the leukocytes but no immature forms. The other considered some of the cells to be lymphoblasts and thought that there were many abnormal lymphoid cells present.

At necropsy the spleen was found to weigh 310 Gm., and the normal architecture was replaced by a firm, gelatinous, gray, glistening tissue. The right ovary

weighed 350 Gm. and the left, 75 Gm. The enlargement of the ovaries and breasts was due to a friable, gray, nodular, cellular growth with hemorrhagic areas. The bone marrow was reddish gray and glistened. There was no enlargement of the lymph nodes.

Microscopic examination showed that the predominant tumor cell had a large, round, vesicular nucleus with a variable amount of somewhat granular cytoplasm. Some of the cells had distinctly lobulated nuclei and some showed definite granules in their cytoplasm. The ovarian tissue, breasts, spleen and gingiva were so densely infiltrated by these myeloid cells that in places no normal structure could be recognized. The cells were supported by a delicate stroma of fibroblastic tissue, and many of them were in mitosis. In the spleen only a few malpighian corpuscles could be seen, and although the sinusoids remained open they were irregular in outline. A few reticular cells containing erythrocytes were found. The fat of the bone marrow was replaced by dense masses of erythrocytes, and myeloid cells and mitoses were numerous. A hemolytic streptococcus was isolated from the heart's blood at necropsy.

TABLE 6.—*Blood Counts in Case 4*

Date	Hemoglobin	Erythrocytes	Leukocytes	Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
9/30/30	50	2,130,000	6,350	..	..	..	..	..	..	..	..	..	..	..	..	..
10/ 2/30	40	1,750,000	5,800	44	..	..	..	..	..	15	..	..	..	41	..	..
10/ 3/30	30	1,500,000	2,500	..	..	..	..	..	..	..	..	..	....	....	....	..
10/ 4/30	30	1,750,000	2,400	30	..	2	..	1	..	15	..	1	..	22	27	2
10/ 6/30	25	1,350,000	2,400	..	..	..	..	..	..	..	..	..	..	..	..	..
10/ 7/30	23	1,510,000	3,600	45	..	16	..	..	..	23	..	..	..	5	8	3
10/ 9/30	30	1,850,000	2,400	32	..	4	..	1	..	6	..	..	..	35	19	3
10/14/30	40	2,150,000	2,600	50	..	..	..	..	2	35	..	..	..	9	3	1
10/18/30	40	3,000,000	2,800	50	..	..	..	..	..	37	..	..	..	8	5	..
11/12/30	..	2,440,000	5,900	55	..	..	..	..	1	27	..	..	..	17	..	..
11/18/30	53	2,910,000	5,400	51	..	..	..	1	1	16	..	6	..	16	9	..
11/30/30	35	1,970,000	17,600	36	..	15	1	..	2	15	..	2	..	23	3	3
12/ 7/30	..	.....	.....	44	..	1	..	..	..	13	..	..	..	40	..	2
12/10/30	33	1,900,000	5,600	..	..	..	..	..	..	..	..	..	..	..	..	..
12/21/30	31	1,790,000	5,200	33	..	1	8	2	..	9	..	..	..	25	22	..

CASE 5.—*Aleukemic myelosis, diffuse type.*

H. S., a white woman, aged 22, was admitted to the University Hospital on Dec. 5, 1930. About June 1, when she was five months pregnant, pain developed in the sacral region which became so severe that labor was induced one month later. Although the sacral pain disappeared, she never regained her normal strength, and subsequently pain and swelling of the ankles, knees, fingers, wrists and elbows developed. In September, small white nodules appeared in the skin over the face and neck. These were firm but not tender and were unduly white as from stretching of the overlying skin. Similar nodules appeared over the entire body, but were most numerous on the forearms and legs. The patient had always bruised easily but had never bled profusely. She was brought to the hospital because of extreme weakness and pallor.

The patient was emaciated, and the skin and mucous membranes were pale. The cervical, axillary and inguinal lymph nodes were enlarged, firm and freely movable, but not tender. The liver was enlarged, and the splenic dulness was

increased. Both breasts contained numerous firm nodules which varied from 0.5 to 1 cm. in diameter. They were freely movable and were not attached to the overlying skin or the nipple. The muscles were small, atrophic and tender to pressure. The skin was thickened and inelastic over the entire body and contained small firm nodules which were almost confluent over the forearms, legs, feet and hands. These nodules seemed to arise from the subcutaneous tissue and deep layers of the skin. After a constrictor had been placed about the arm, hemorrhages appeared at the periphery of each nodule. Irradiation (136 kilovolts, 4 milliamperes, 50 cm. skin target distance with a filtration of 3 mm. of aluminum, which gave 200 roentgens in eighteen and a half minutes) was given over a small area on the forearm. The size of the nodules in this area decreased about 75 per cent within seventy-two hours.

Fig. 2 (case 5).—Cutaneous nodules on the forearm and face.

The urine did not contain Bence-Jones protein, but there was a trace of albumin. The Wassermann reaction was negative. The results of several examinations of the blood are recorded in table 3. The blood calcium was 11 mg., the phosphorus 4.08 mg. and the plasma cholesterol 192.3 mg. per hundred cubic centimeters. The basal metabolic rate was 70 and 66 per cent above normal on two successive days but the temperature was 100 F. on each occasion.

Roentgenologic examination of the skeleton showed areas of calcium absorption and some subperiosteal proliferation parallel to the long axis of the bones. Perpendicular spicules were found, particularly at the tendon and muscle attachments on the femora, ischia, pubes, radii and ulnae and in the metacarpals. The lesions in the spine showed more of an osteoblastic type of reaction, but there were also areas of calcium absorption. The cranial bones showed multiple pinpoint areas of decalcification.

The thickened inelastic and tightly drawn skin, as well as the atrophic and tender muscles, suggested a diagnosis of dermatomyositis, but this was obviously untenable in the face of the other findings.

The roentgenologic changes in the bones, the nodules on the skin and breast and even the microscopic appearance of the skin and a lymph node removed for biopsy were suggestive of carcinomatosis. However, the splenomegaly (which is rare in carcinoma), the multiple tumors of the breast, the marked increase in the consumption of oxygen and the almost miraculous response of the cutaneous tumors to

Fig. 3 (case 5).—Perpendicular spicules of bone at the lower end of the femur.

irradiation led to a clinical diagnosis of a hematopoietic disease. Necropsy left no doubt as to the correctness of this impression.

The course of the patient's condition was progressively downward, and she died at her home on December 28.

Necropsy was performed by Dr. A. B. Konwaler of Davenport, Iowa, who turned the tissue over to us for study. The myocardium was pale, and a small white nodule was noted beneath the epicardium of the left ventricle. The pericardium was thickened and adherent to the pleura and several hemorrhagic lymph nodes were attached to it. The mediastinal lymph nodes were enlarged. The normal architecture was lost, the hilus obliterated and the tissue had the grayish, granular appearance of great cellularity. The spleen was enlarged, grayish and friable, and contained one large scar. The liver was enlarged, light in color and friable, and contained

numerous round nodules, some of which were white and others hemorrhagic. The largest nodule measured 4 cm. in diameter. The kidneys were large, and the capsule stripped easily, leaving a nodular hemorrhagic surface. They were pale on cut section and contained scattered hemorrhagic areas.

The abdominal and retroperitoneal nodes were greatly enlarged and loosely matted together. They were firm and on cut section presented a smooth gray surface with scattered areas of hemorrhage. The periosteum of the ribs was thickened and that of the femur was roughened and contained round, white, dense areas and also some yellowish mottling. The bone marrow of the femur was grayish red.

Fig. 4 (case 5).—A portion of the skull showing the multiple pinpoint areas of decalcification.

Microscopic examination showed the "infiltrating" cells which appeared in nearly every tissue to be from two to three times the diameter of an erythrocyte. The nuclei were round, oval or lobulated, and many contained nucleoli. The cells had an abundant cytoplasm which was usually molded by their close apposition. In some, the cytoplasm was stippled with fine granules, part of which were eosinophilic. A few cells with basophilic granules were found. Mitotic figures were numerous, and some cells were multinucleated.

The heart showed a moderate perivascular infiltration by cells of the type described, and the nodule described grossly consisted of densely packed cells infiltrating the cardiac muscle. Sections of the lungs showed no infiltration.

The spleen was, for the most part, packed with the large myeloid cells, and only an occasional adult neutrophil or lymphocyte was seen. A few multinucleated cells and a few mitotic figures were seen. An occasional nucleated erythrocyte was found.

Lesions of two types were found in the liver. In the first there was a nodular mass of hematopoietic cells growing so as to compress the liver cords and produce degenerative changes in the hepatic cells. The second type of lesion consisted of a dense infiltration of the sinusoids of the liver, and in these areas more adult neutrophils were present.

The kidneys showed a marked infiltration by hematopoietic cells. A similar infiltration was present in the ovary, uterus, trachea and other structures. In the breasts there was a marked fibroblastic reaction, which caused the cells to form into cords and layers. In the lymph nodes the follicles were compressed by the hematopoietic cells, and multinucleated cells were frequent.

In the skin these cells were collected in groups and cords and had invaded the deeper layers of the skin and subcutaneous fat.

TABLE 7.—*Blood Counts in Case 5*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/ 5/30.....	39	2,370,000	6,840	13	1	..	11	..	1	1	43	..	..	..	4	..	26
12/ 6/30.....	..	.....	.....	6	11	5	8	2	1	5	32	..	1	..	6	5	18
12/13/30.....	34	2,020,000	8,100	4	3	9	6	1	2	3	4	..	..	..	18	25	25
12/18/30.....	33	2,150,000	11,600	5	8	5	17	..	1	3	10	1	..	..	9	15	26

The cortex of the bone showed marked sclerosis, while the marrow spaces were rich in cells. There was infiltration of the periosteum of the ribs, and the marrow of both the ribs and long bones was filled with the myeloid cells. The marrow of the long bones contained more erythrocytes and erythroblasts than that of the ribs.

CASE 6.—*Aleukemic myelosis, diffuse type.*

J. W., a white girl, aged 11 years, was brought to the University Hospital on Jan. 15, 1931, because of anemia, weakness and loss of weight which began five months prior to her admission. During September, 1930, she had an attack of vomiting, diarrhea and fever of three days' duration, following which she received four blood transfusions. Following the last transfusion, she had a fever and severe hemorrhages from the nose. She had attacks of pain and swelling which migrated from one joint to another until practically every joint in the body had been involved.

Examination revealed marked pallor, weakness, bloody crusts in the nose and excoriations of the soft palate. The anterior cervical, axillary and inguinal lymph nodes were palpable. There was dulness with suppression of breath sounds at the base of the right lung. The liver was not palpable, but the spleen was tender and extended 3 cm. below the costal margin. The ankles and wrists were tender and motion was painful. She became worse in spite of repeated blood transfusions, and hemorrhages from various areas became a prominent feature. She died on February 2. Permission for necropsy was not obtained.

The urine was normal. The Wassermann and tuberculin tests were negative. Before admission the leukocyte count had varied from 1,200 to 4,000 per cubic millimeter, and there were from 8 to 11 nucleated erythrocytes to every 100 leukocytes. The blood cultures remained sterile. The results of the blood studies are recorded in table 3. The blood cholesterol was below 10 mg. per hundred cubic centimeters. The blood calcium was 9.7 mg. and the phosphorus 3.9 mg. per hundred cubic centimeters.

Roentgenograms of the skeleton showed evidence of rarefaction of the distal ends of the femora, tibiae and left radius and ulna. Similar changes were seen in the metacarpals and phalanges. No disturbance of the architecture of the bone was present, and the trabeculations were not increased. There was some thinning of the cranial vault, with a generalized loss of calcium from the pelvis.

A cervical lymph node was removed. There was a hemorrhagic area beneath the capsule, and on cut section the surface was smooth, gray and granular. The

TABLE 8.—*Blood Counts in Case 6*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/ 8/30.....	22	1,500,000	9,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/ 9/30.....	32	1,960,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/10/30.....	34	1,900,000	3,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/11/30.....	32	1,880,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/12/30.....	30	1,850,000	2,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/13/30.....	34	1,500,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/15/30.....	20	1,490,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/16/30.....	22	1,400,000	3,500	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/17/30.....	28	2,000,000	4,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/21/30.....	30	2,000,000	3,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
12/22/30.....	34	1,500,000	2,500	13	15	..	9	8	..	2	11	..	16	13	..	6	7
1/16/31.....	35	1,240,000	16,000	7	8	..	10	12	1	..	35	5	4	14	..	3	1
1/19/31.....	..	.....	6,900	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1/23/31.....	45	2,840,000	7,400	7	19	..	18	5	1	4	4	1	7	25	..	7	2
1/25/31.....	40	2,800,000	5,500	19	29	..	14	5	2	3	3	1	..	18	..	6	..
2/ 1/31.....	35	1,950,000	2,600	..	..	..	..	..	..	..	..	..	..	..	..	..	..

normal architecture could not be distinguished grossly or histologically. The sinuses were filled with cells, and no germinal centers were visible. The cytoplasm of the predominant cell contained granules, and the nuclei were large and vesicular. Few of the cells contained polymorphic nuclei. Many mitotic figures were present, and there were numerous eosinophils. The tissue was made up of hematopoietic cells, most of which appeared to be very young, and the granules suggested their myelocytic nature. The pathologic diagnosis from the biopsy specimen was myelosis.

Examinations of the blood prior to this patient's admission to the University Hospital were made by Dr. H. W. Rathe. Blood smears for this period were examined by one of us and were found to contain numerous erythroblasts but no other young cells and few abnormal leukocytes. Actual differential counts were not made. In this case, also, there were no definite myelocytes, since the cells which resembled myelocytes in other respects were nongranular. The "blast cells" were also of questionable classification in that they did not appear to contain nucleoli. The leukocytes were similar to those in case 4.

CASE 7.—*Multiple myeloma, myeloid type?; aleukemic myelosis, diffuse type?* I. M., a white woman, aged 52, was admitted to the University Hospital on Aug. 24, 1932, because of pain in the lower part of the back and loss of strength. The weakness was first noticed about ten months prior to her admission and gradually progressed until it became the most prominent symptom. Six months prior to admission pain developed over the upper part of the chest which seemed to migrate to the back and persisted in two areas just medial to the scapulae. The patient was forced to be extremely careful when bending over, but continued with her housework until two months prior to her admission, when she fell and was unable to arise because of pain in the lumbar region. The following morning she had a severe cramp in the muscles of the lower part of the back and was unable to straighten up. This pain and muscle spasm gradually subsided during the next two months, but her weakness became so extreme that she was confined to her bed.

The patient was very pale but not icteric. The skin was dry, and there was evidence of much loss of weight. There was no lymphadenopathy, although the

TABLE 9.—*Blood Counts in Case 7*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
8/24/32.....	44	1,710,000	6,950	36	12	..	..	..	..	1	44	..	2	..	..	5	..
9/10/32.....	32	1,560,000	6,000	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9/19/32.....	21	1,220,000	5,100	..	..	..	..	..	..	..	..	..	..	..	..	..	..
9/21/32.....	..	.....	.....	32	8	..	..	..	..	1	42	..	8	3	1	5	..
9/22/32.....	25	1,550,000	6,300	30	12	..	..	..	..	1	43	..	8	1	1	4	..
10/ 3/32.....	26	1,450,000	5,050	44	4	..	..	1	..	1	38	1	7	..	..	4	..
10/ 7/32.....	30	1,580,000	.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10/10/32.....	35	2,240,000	5,300	..	..	..	..	..	..	..	..	..	..	..	..	..	..
10/17/32.....	39	2,260,000	4,500	30	27	1	..	..	..	..	16	..	2	14	..	10	..

spleen extended 3 cm. below the costal margin and the edge of the liver was palpable. The lungs were clear, and the heart normal except for a hemic murmur. The blood pressure was 144 systolic and 72 diastolic. There was slight tenderness over the lumbar spine and a tender thickening could be felt over the sixth rib on the left in the anterior axillary line. There was no other bony tenderness.

Roentgenograms of the skeletal system revealed multiple, rounded, sharply defined osteolytic areas involving the skull, ribs, pelvis, second lumbar vertebra, left humerus and femora. Roentgenologic examinations of the gastro-enteric and genito-urinary tracts gave negative results. The urine contained some albumin and a few granular casts. Bence-Jones protein was found in the urine on one occasion. The Wassermann reaction of the blood was twice anticomplementary and the Kahn test was negative, as was the Wassermann reaction of the spinal fluid. The van den Bergh test was negative on two occasions. The specific gravity of the urine varied from 1.009 to 1.013, and the urinary output during the night slightly exceeded that during the day. The excretion of dye was 10 per cent in two hours, and the urea clearance was 26 per cent of normal, but there was no retention of nonprotein nitrogen in the blood. The basal metabolic rate was 25.7, 15.6, 17.5 and 21 per cent above normal on different days.

At different times and by different chemists the blood calcium was found to be 16.7, 17.1 and 16 mg. per hundred cubic centimeters. The serum calcium was 15 mg. and the spinal fluid calcium, 6.5 mg. Urinary calcium for a twenty-four hour period was 768 mg., while the value for phosphorus was 589 mg. The blood phosphorus (inorganic) was also determined by three chemists, the values being 2.8, 2.66 and 3.1 mg. The serum phosphorus was 3.5 and 3.8 mg. The total phosphorus of whole blood was 26.7 mg. and of the serum, 10.4 mg. The hematocrit reading at the time of these determinations was 15 per cent. The serum protein was found to be 12.3 per cent (albumin, 1.5 and globulin 10.8 per cent),

Fig. 5 (case 7).—Multiple rounded osteolytic areas in the skull.

and a week later it was 10.3 per cent (albumin 1.4 and globulin 8.9 per cent). Another determination by another laboratory after a lapse of a week showed plasma protein 7.43 per cent (fibrinogen 0.51, albumin 1.56 and globulin 5.36 per cent). The serum cholesterol was found to be 82 and 62 mg. per hundred cubic centimeters on two occasions, while the plasma cholesterol was 113.6 mg. a week later.

A biopsy was made from one of the lesions in the skull. There was a clean-cut lytic lesion which had penetrated neither the outer nor the inner table completely. The bone about the lesion appeared normal. The soft tissue removed was gray, finely granular and friable and appeared to be extremely cellular on

gross examination. Microscopic examination revealed the tissue to be very cellular, the predominating cell being moderately large with a light-staining, round, vesicular nucleus which was notched in some cells. The cytoplasm was pink (hematoxylin-eosin stain) and was not abundant. Several mycotic figures and a few megakaryocytes were seen. The diagnosis was the myeloid type of multiple myeloma.

The patient was discharged from the hospital at the request of relatives.

CASE 8.—*Multiple myeloma, myeloid type.*

C. N., a white woman, aged 63, was admitted to the University Hospital on Dec. 16, 1930, because of severe pain in the right shoulder and left hip. This pain began in the left hip in the summer of 1929 and was sharp and shooting, but did not radiate, and the area had never been discolored or swollen. A similar pain appeared in the right shoulder and was present even with the part at rest.

There was severe pain in the right shoulder on the slightest motion, but there was no swelling or crepitation, and passive motion was restricted only because

TABLE 10.—*Blood Counts in Case 8*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
12/16/30.....	69	4,000,000	11,550	63	8	..	1	..	..	4	17	..	5	1	1	..	..
12/31/30.....	..	.....	15,800	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1/ 7/31.....	..	.....	12,400	..	..	..	..	..	..	..	..	..	..	..	..	..	..
1/30/31.....	56	3,920,000	12,600	45	30	..	1	..	..	1	16	..	3	3	1	..	..
2/ 7/31.....	61	3,920,000	8,650	37	26	..	..	..	..	2	..	..	12	23	..	..	..
3/ 7/31.....	59	3,930,000	5,850	67	4	..	..	..	..	..	8	..	10	7	4	..	..

of the pain. The reflexes were normal, but there was some atrophy of the intrinsic muscles of the right hand. The left thigh was held flexed and adducted, and there was severe pain on motion but no crepitation. There was some pain over the adductor muscles. The spleen and lymph nodes were not enlarged.

The urine showed a trace of albumin, but no Bence-Jones protein could be found. The Wassermann reaction was negative. The results of examinations of the blood are shown in table 3. The blood calcium was 8.6 mg. and the blood phosphorus 4.3 mg. per hundred cubic centimeters. The basal metabolic rate was found to be 7.9 and 7.6 per cent below normal on two occasions. The blood cholesterol was 94.7 mg. per hundred cubic centimeters. Pelvic examination and roentgen examinations of the gastro-enteric and urinary tracts gave negative results. Roentgenograms of the right scapula showed a large area of destruction, purely osteolytic in type, and there were similar lesions in several of the ribs. There were multiple large areas of destruction in both sides of the pelvis, in the lesser trochanter on the right femur and in the greater trochanter on the left femur. Roentgenograms taken one year previously showed a less extensive destructive lesion involving the greater trochanter on the left.

The pain persisted in spite of repeated irradiation over the involved areas. The patient became progressively weaker and died on March 22, 1931. Permission for necropsy was refused.

A biopsy was made from the lesion in the right scapula. This showed dense fibrous tissue with areas composed of large pale-staining cells with a granular cytoplasm and vesicular nuclei. Some of these cells were in mitosis. There were many lymphocytes and a striking number of eosinophils in the lesion, but the predominant cell was of myeloid origin.

Comment.—Although absolute proof is wanting, it seems fair to infer that in this case the myelosis was of the localized form. The long duration, the localized bony defects and the almost complete lack of abnormalities in the peripheral blood all strongly suggest that the bone marrow was not diffusely involved.

This process is, of course, closely related to the ordinary type of multiple myeloma of the plasma cell type.

CASE 9.—*Myeloma, extramedullary.*

D. B., a white girl, aged 16, was admitted to the University Hospital on Jan. 27, 1932, because of a protrusion of the right eye. In September, 1931, she first noticed some swelling of the right cheek which receded after the application of heat. She had no further trouble until three weeks prior to her admission, when exophthalmos of the right eye was noticed. This gradually increased, but there was no visual disturbance or pain associated with the protrusion.

There was a marked exophthalmos of the right eye, but the ocular motions were normal. The right eye was distinctly higher than the left, and a hard mass was felt at the junction of the inferior with the lateral rim of the orbit. The remainder of the physical examination gave negative results.

Roentgenologic examination of the orbital region showed a small tumor in the soft tissue, but there was no evident defect in the bone.

A biopsy was made from the tumor mass, and the pathologic report stated that this consisted of fibrous tissue which was infiltrated with lymphocytes, plasma cells and endothelial cells without any regularity of distribution. There were also many cells with a polymorphic type of nucleus, and these appeared to belong to the myelocytic series. Myeloid cells were present in such numbers that it was felt that the tumor was of myeloblastic origin, and the diagnosis of myeloblastoma was made.

Roentgen therapy was applied to the region of the tumor for a period of twelve days during which the patient received 2,400 roentgens. Following this the tumor was removed surgically, and radium needles were inserted at the time of operation.

During the course of treatment she complained of pain in the right knee and ankle, and a purpuric rash appeared over both legs extending up to the trunk. There was a slight swelling of both the right knee and ankle without redness or local heat, although the joints were extremely painful. The patient had experienced an identical episode about one year previously.

The urine showed an occasional finely granular cast and a trace of albumin. The Wassermann reaction was negative. Special blood tests are shown in table 3.

Two other children were encountered with clinical manifestations almost identical to those in this case. Biopsy of a specimen from the orbital tumor was made in each instance, and both growths were found to be hematopoietic tumors, but myeloid cells did not predominate in either. Lymphoid and undifferentiated cells predominated in one, and in the other the tumor cells were undifferentiated,

but a myelophthisic anemia and changes in the roentgenograms of the pelvic bones indicated that the bone marrow was being invaded.

CASE 10.—*Myeloma, extramedullary.*

I. C., a white man, aged 36, was admitted to the University Hospital on Jan. 15, 1926, because of loss of strength and the presence of a nodule on the left wrist. The illness began with pain in the right arm in March, 1923, and in December, 1923, the arm became weak and numb. In March, 1924, a nodule appeared at the right elbow and another at the right wrist. These were not painful except after injury. The tumors were removed in September, 1924, but recurred, and in January, 1925, were again removed together with a piece of bone from the right wrist. In June, 1925, a similar nodule appeared on the left wrist. He had noticed some loss of strength during the year 1925.

TABLE 11.—*Blood Counts in Case 9*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Questionable Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
3/ 9/32.....	80	4,140,000	8,200	68	6	..	2	..	..	4	9	..	6	2	..	3	..
3/11/32.....	85	4,190,000	12,400	73	4	..	..	..	..	2	17	..	4	..	..	..	..

TABLE 12.—*Blood Counts in Case 10*

Date	Hemoglobin	Erythrocytes	Leukocytes	Segmented Neutrophils	Band Neutrophils	Metamyelocytes	Myelocytes	Blast Cells	Basophils	Eosinophils	Lymphocytes	Türk Irritation Cells	Monocytes	Abnormal Mononuclears	Unclassified	Degenerated Cells	Erythroblasts
1/15/26.....	80	2,660,000	2,600	74	..	..	..	..	..	..	26	..	..	..	..	..	..
1/18/26.....	50	3,250,000	.....	60	..	..	..	..	..	..	22	..	18	..	..	..	..
1/24/26.....	60	3,480,000	14,400	..	..	..	..	..	..	..	..	..	..	..	..	..	..

The results of general physical examination were not remarkable. There were linear scars over the right elbow and wrist and there was atrophy of the intrinsic muscles of both hands. On the radial side of the left wrist was a spindle-shaped nodule 5 by 2.5 cm. This was tender, and pain radiated both distally and proximally from the growth. The mass was not attached to the underlying structures except at the two poles, and the skin was movable over the tumor mass. There was a loss of pain and thermal sensations and a partial pallanesthesia on the radial aspect of the left hand.

The tumor was removed surgically and was found to follow the course of a superficial nerve. Fever developed the second day after the operation, and the patient died in coma on January 24.

Roentgen examination of the skeletal system gave negative results. The Wassermann reaction was negative. A lumbar puncture, the day after admission, showed 13 cells per cubic millimeter and a 1+ globulin reaction. The urine was normal.

Examination of the brain at necropsy revealed an acute streptococcic encephalitis. The heart, lungs, liver and kidneys were normal on both gross and microscopic examination. The spleen weighed 350 Gm. The color was more of a bluish tint than normal, and the spleen was soft in consistency. On cut section the pulp appeared cellular, and the malpighian bodies were more prominent than normal. Microscopic examination revealed the pulp to be infiltrated and the venous sinuses filled with cells of the granulocytic series, mainly myelocytes and myeloblasts.

The lymph nodes were not enlarged, and on microscopic examination only a healed tuberculous lesion was found in the mediastinal glands. The bone marrow was not examined.

The tumor removed surgically was not encapsulated and appeared grayish, opaque and very cellular. The stroma was made up chiefly of blood vessels and supporting connective tissue. In the majority of the cells the nuclei were deep-staining and were frequently bilobed; a few were multinucleated. The cytoplasm was eosinophilic with hematoxylin-eosin. It was evidently of bone marrow origin, and the pathologist's diagnosis was myeloblastoma.

COMMENT

Cases of true aleukemic myelosis are not numerous in the American literature, but the frequency of their actual occurrence can best be adjudged from studies of the type presented in table 1. About 5 per cent of our cases of diffuse myelosis were permanently aleukemic. Most physicians seem to regard aleukemic myelosis as an obscure form of hematopoietic disease which can be diagnosed only at necropsy. Certainly acceptable criteria for an accurate clinical diagnosis have not been established.

We have accepted the term "myelosis" because it refers to a more fundamental hematopoietic change than does "leukemia," and at the same time avoids the necessity for using such an inherently contradictory term as "aleukemic leukemia."

Two cases of tumors of the bone marrow, as well as two cases of extramedullary tumors composed of myeloid cells are included in this series. The growths in the former two cases are classified as multiple myelomas (myeloid type) because they appear to have more in common with ordinary multiple myeloma of the plasma cell type than with the diffuse forms of myelosis. The extramedullary myeloid tumors resembled the bone marrow type histologically, but the clinical manifestation differed. The latter have been called myelomas.

DIFFUSE ALEUKEMIC MYELOSIS

The relationship between permanently aleukemic myelosis and either spontaneous or induced aleukemic periods in leukemic myelosis is not clear. In spite of more or less plausible theories, the actual explanation for the transfer of cells from the fixed hematopoietic tissue to the cir-

culating blood has never been discovered.[3] It is possible that the aleukemic period in case 1 resulted from rather intensive irradiation of the spleen. The skeleton was not irradiated, so that the effect on the bone marrow must have been indirect. It is almost inconceivable, however, that the small amount of irradiation administered to the right cheek in case 2 could have influenced the development of the aleukemic period which followed.

Aleukemic and leukemic myelosis present similar histologic changes.[4] In the aleukemic cases reported by Pinkerton [4b] the leukemic infiltration was quantitatively somewhat less than in ordinary leukemic myelosis. In our cases 3, 4 and 5 the gross and microscopic appearance of the bone marrow and parenchymatous organs did not differ either qualitatively or quantitatively from the appearance in the leukemic form. Clinically, however, there are differences in these two forms of diffuse myelosis even though the differences may not be of fundamental importance. The aleukemic form of myelosis is often more rapidly fatal than the leukemic form, the associated anemia is often more marked and the likelihood of secondary hemorrhagic purpura is greater, but the aleukemic form is of special interest, mainly because it presents certain definite diagnostic difficulties.

Changes in the Formed Elements of the Peripheral Blood in Diffuse Aleukemic Myelosis.—In true aleukemic myelosis not only is there an absence of leukocythemia but the differential formula also approaches the normal.[5] In our own cases the degree of abnormality of the blood smear was more or less dependent on the thoroughness with which it was scrutinized from day to day. Certainly a diagnosis could not be made from the blood smear alone in these cases, and some of the stained films might pass as normal on a casual examination. However, to call the blood smears in our cases of diffuse aleukemic myelosis absolutely and consistently normal would be to overstate the facts. One or more of the following abnormalities were encountered in the smears from each of the cases: a leukopenia, a shift to the left in the granulocytes to include a few metamyelocytes and an occasional questionable myelocyte, an abnormal number of basket cells or naked nuclei, bizarre cells which we were unable to classify, occasional erythroblasts or a thrombocytopenia. It is realized, of course, that none of these changes are in any

3. Isaac, R.: The Physiologic Histology of Bone Marrow, Folia haemat. **40**:395, 1930. Doan, C. A.: The Neutropenic State, J. A. M. A. **99**:194 (July 16) 1932.

4. (*a*) Jaffe, R. H.: Aleukemia Myelosis, Arch. Path. **3**:56 (Jan.) 1927. (*b*) Pinkerton, H.: Aleukemic Leukemia and Atypical Leukemoid Conditions, Arch. Path. **7**:567 (April) 1929.

5. Mosse, M.: Zur Geschichte der "aleukämeschen Myelose," Centralbl. f. allg. Path u. path. Anat. **50**:337, 1931. Jaffe.[4a]

way specific for aleukemic myelosis, since the same changes may be seen in metastatic tumors involving bone marrow,[6] in osteosclerosis[6] and in sepsis.[7]

Anemia unexplained by either hemorrhage or hemolysis is a prominent feature in the diffuse form of aleukemic myelosis. We know of no explanation for the fact that the anemia in aleukemic myelosis may be more profound and may develop more rapidly than that of the leukemic form. Hemorrhage from the uterus contributed generously to the anemia in case 4. However, there was no excess bleeding in case 5, and in case 6 the anemia was grave before the nasal hemorrhages occurred. The anemia is not aplastic, as evidenced by the increase in reticulocytes. In this form of acute myelophthisic anemia the color index may be above unity, perhaps because there is no shortage of materials for the production of hemoglobin, while there is a paucity of space in which the stroma for new cells may develop. Confusion might occur between aleukemic myelosis and pernicious anemia because of the high color index, the leukopenia and the anemia which are common to both diseases.

The thrombocytes were greatly decreased in our cases of diffuse aleukemic myelosis. This may have been on a myelophthisic basis, but an increase in platelets is found throughout most of the course in leukemic myelosis, and the crowding appears to be equally great in both diseases. The regularity and diagnostic importance of these changes in platelets can be determined only by the study of more cases.

The results of further blood studies are shown in table 3. It is apparent from these studies that the laboratory tests for purpura haemorrhagica (long bleeding time, nonretractile clot, positive arm band test and thrombocytopenia) were positive in the three cases of diffuse aleukemic myelosis in which they were done. In this respect the aleukemic differs from the leukemic form of myelosis. Spontaneous ecchymoses and petechiae occurred in all three cases. Experiences such as these have led us to formulate for ourselves certain rigid criteria which must be fulfilled before we advise splenectomy for purpura haemorrhagica. We do not advise splenectomy unless the four laboratory tests previously mentioned are positive in a case in which there is a history of remissions and in which all hematopoietic diseases which lead to secondary purpura haemorrhagica have been excluded. In the cases of idiopathic purpura haemorrhagica which we have observed, remissions were induced relatively easily by transfusion, but this was not true of the cases of secondary hemorrhagic purpuras.

6. Mavros, A.: Aleukämische, besser "nichtleukämische" Myelose mit Osteosklerose, Folia haemat. **43**:323, 1931.

7. Krumbhaar, E. B.: Leukemoid Blood Pictures in Various Clinical Conditions, Am. J. M. Sc. **172**:519, 1926.

Roentgenologic Findings.—Roentgenograms were of considerable value in the diagnosis of our cases. Case 4 showed an area of calcium absorption in the mandible. In case 5 there were widespread proliferative as well as some osteolytic changes in the skeleton, and a less marked loss of calcium was a feature in case 6. The roentgenologic changes in diffuse aleukemic myelosis might be confused with those of metastatic carcinoma, multiple myeloma of any type or lymphoma with metastases to the bone. The changes in the bone in hyperparathyroidism may be simulated to some degree in diffuse aleukemic myelosis.

Consumption of Oxygen.—The consumption of oxygen is usually increased at some time during the course in all types of leukemia. Case 4 (basal metabolic rate, — 1.4 and + 23 per cent) and case 5 (basal metabolic rate + 66 and + 70 per cent) tend to show that aleukemic myelosis is no exception to the general rule.[8] If the increase in metabolism proves to be more marked in aleukemic myelosis than in metastatic tumors of the bone marrow (as it has in our experience), it will, of course, be an aid in the clinical diagnosis of the disease.

Biopsy.—It is possible that we were unusually fortunate in having suitable biopsy material present itself in our cases. In case 4 material was removed from the margin of the gums; in case 5 from the skin and a lymph node, and in case 6 from a lymph node. Had not these more available materials presented themselves, we should have taken bone marrow (as in cases 7 and 8)—a procedure which we have found to be relatively simple and harmless. The demonstration of hyperplastic gray tissue in areas which are normally fatty in the adult is an important step in establishing a diagnosis of aleukemic myelosis. Microscopic studies should be done by the method of Isaacs[9] as well as by means of sections.

Other Less Constant Symptoms and Observations.—Manifestations in the joints not unlike those seen in rheumatic fever occurred in cases 5 and 6. One of us (Dr. Baldridge[10]) previously reported a series of cases of lymphatic leukemia in which 63 per cent of the patients under 21 years of age showed similar symptoms in the joints. It is regrettable that the nature of the changes in the joints could not have been investigated at necropsy.

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8. Baldridge, C. W., and Barer, A.: Studies on the Relationship Between Oxygen Consumption and Nitrogen Metabolism: II. In Leukemia, Arch. Int. Med. **51**:589 (April) 1933.

9. Isaacs, R.: Alterations of Tissue Cells in the Blood Stream, Science **68**: 547, 1928.

10. Baldridge, C. W., and Awe, C. D.: Lymphoma, Arch. Int. Med. **45**:161 (Feb.) 1930.

Tumefaction of the gums and numbness of the chin, such as occurred in case 4, are not rare in myelosis or in monocytic leukemia, but are uncommon in other dyscrasias of the blood. Areas of calcium absorption from the mandible like that seen in case 4 are at times demonstrable in leukemic myelosis. Either of these findings should cause the physician or dentist to be on his guard, since the extraction of teeth may be a fatal error in chronic leukemia and is rarely, if ever, justified in acute exacerbations of the chronic forms or in acute blast cell leukemia.

The urine in cases 4, 5 and 6 was examined for Bence-Jones protein with negative results. In cases 5 and 6 in which the roentgen changes in the bones were extensive enough to suggest a metabolic disturbance such as hyperparathyroidism, the calcium and phosphorus of the blood were normal. The calcium and phosphorus balances were not determined. We know of no explanation for the extremely low plasma cholesterol in case 6.

Terminal or postmortem blood cultures yielded Streptococcus haemolyticus in cases 3 and 4 and Staphylococcus albus in cases 5 and 6. These instances of septicemia appeared to be of the ordinary terminal variety. The exact degree of hyperplasia, metaplasia and anaplasia which distinguishes primary hematopoietic disease from response to infection may be a matter of personal opinion in borderline cases. The hyperplasia of the bone marrow which was associated with absorption of cancellous bone and the "leukemic infiltration" which were present in these cases excluded to our satisfaction the possibility that the hematopoietic change was an unusual response to ordinary infection.

MULTIPLE MYELOMA, MYELOID TYPE

Cases 7 and 8 would have been diagnosed multiple myeloma, and it would have been assumed that the tumors were of the plasma cell type had not biopsies been made. It must be admitted that we have no proof that the bone marrow was not diffusely involved in case 7 or even in case 8. It must also be admitted that we have no proof that the whole bone marrow was involved in the patient whose condition was diagnosed diffuse aleukemic myelosis. Indeed, one can see here almost every gradation from ordinary leukemic myelosis to single extramedullary tumors made up of myeloid cells. The subdivisions which we have made are for convenience and not because we are convinced that they are warranted. The criteria for the clinical diagnosis for patients assumed to have localized lesions in the bone marrow differ somewhat from the findings in those in whom a diffuse hyperplasia of the bone marrow seemed more likely. In cases 7 and 8 the blood smears were nearly normal, and secondary hemorrhagic purpura was

not present. Anemia was marked in case 7 but not in case 8. Roentgenograms gave positive evidence of lytic lesions in both. The consumption of oxygen was increased in case 7, but was in the low normal range in case 8. The disease process was considerably more widespread and more active in the former case.

Quantitative determinations of the various constituents of the blood are of considerable diagnostic value in a few of the cases in this group. Plasma proteins may be markedly abnormal, as demonstrated in case 7. Perlzweig, Delrue and Geschickter [11] reported a case of multiple myeloma of the plasma cell type in which the globulin fraction was found to be 11.04 per cent on one occasion. Shirer, Duncan and Haden [12] reported two cases of myeloma in which an apparent increase in globulin was proved to be due to Bence-Jones protein in the plasma. Our case 7 and that of Perlzweig and his associates, as well as one of Shirer's cases, showed Bence-Jones proteinuria. Reimann [13] reported a case of multiple myeloma (plasma cell type) in which the total plasma protein was 10.12 per cent, of which 5.48 per cent was fibrinogen, 2.37 per cent euglobulin, 1.47 per cent pseudoglobulin I and II and 0.9 per cent albumin. The urine did not contain Bence-Jones protein. This patient's serum produced rapid rouleau formation in his own as well as in various donor's corpuscles, so that blood grouping, as well as erythrocyte counting, was impossible. The rapid rouleau formation was attributed by the author to hyperproteinemia. In our case 7 there was no special tendency to rouleau formation, but the Wassermann reaction of the blood was twice anticomplementary.

The blood calcium was repeatedly determined in case 7 with the following findings in milligrams per hundred cubic centimeters: 17.1, 16.7, 16 and 15. Phosphorus was found to be 2.66, 2.8, 3.5 and 3.8 mg. per hundred cubic centimeters. In a patient with carcinomatosis of the bone marrow from carcinoma of the stomach, Dr. C. Van Epps of this hospital found the blood calcium to be 18.5 mg. and the blood phosphorus 4.6 mg. Snapper [14] thinks that hypercalcemia points to hyperparathyroidism only if hypophosphatemia is also present. In cases 5, 6 and 7, the blood calcium and phosphorus values were normal. The urinary calcium in case 7 was much increased, but determinations were

11. Perlzweig, W. A.; Delrue, G., and Geschickter, C.: Hyperproteinemia Associated with Multiple Myelomas, J. A. M. A. **90**:755 (March 10) 1928.

12. Shirer, J. W.; Duncan, W., and Haden, R. L.: Hyperproteinemia Due to Bence-Jones Protein in Myelomatosis, Arch. Int. Med. **50**:829 (Dec.) 1932.

13. Reimann, H. A.: Hyperproteinemia as a Cause of Autohemagglutination: Observations in a Case of Myeloma, J. A. M. A. **99**:1411 (Oct. 22) 1932.

14. Snapper, I.: Calcium and Inorganic Phosphates of the Serum in Hyperparathyroidism and Myeloma, Acta brevia neerland. **1**:25, 1931; abstr., Nutrition Abstr. & Rev. **1**:470, 1932.

not made in the other cases. The level of the blood calcium may parallel the destruction of the bone, but we have no proof of this fact. The lesions of the bone may not have been progressing in the patients with normal levels of blood calcium, but this fact could have been better ascertained had we studied the calcium balance. The plasma cholesterol was moderately decreased in cases 7 and 8.

EXTRAMEDULLARY MYELOMAS

Cases 9 and 10, though not exhaustively studied, failed to show any of the chemical or cytologic abnormalities which were seen in the other groups.

It is to be regretted that our patients were not all studied completely. Patients such as these present a number of interesting abnormalities, and the changes are most interesting because they are so inconstant. We have expended most of our efforts in an attempt to establish criteria for a clinical diagnosis in these cases, since it is obvious that unless the diagnosis can be made clinically, metabolic studies will be impossible.

In the absence of a leukemic blood picture, the following circumstances should suggest the possibility of a hematopoietic disease of the types under discussion:

1. A severe unexplained anemia with a color index of about 1 and with a moderate increase in reticulocytes.

2. Hemorrhagic purpura which does not respond to transfusions of blood.

3. Tumefaction of the gums.

4. Unexplained enlargement of the spleen or lymph nodes.

5. Symptoms of arthritis without selective atrophy of the muscles, increased tendon reflexes or palpable changes in the joints.

6. Nerve root or deep bony pain.

7. Lytic lesions in bones (for example, lesions of the ribs seen in a roentgenogram of the chest).

8. A leukopenia with a shift to the left in an afebrile patient.

9. Erythroblasts found unexpectedly in a smear.

10. Pathologic fractures.

11. High consumption of oxygen in a patient without fever or exophthalmic goiter.

12. Unexplained acute enlargement of the breasts or ovaries.

Of less moment are the following:

1. Reddish-gray nonliquefied tissue discovered at operation for osteomyelitis.

2. Priapism.
3. Abnormally high plasma globulin or fibrinogen.
4. Unexplained hypercalcemia or hypocholesteremia.
5. Bence-Jones proteinuria.
6. Abnormally rapid rouleau formation (Reimann).
7. Unexplained anticomplementary Wassermann tests.

A complete study of a patient with aleukemic myelosis, either diffuse or localized, would require a considerable amount of laboratory and metabolic work. The same is true of multiple myeloma of the plasma cell type. The confused state of our information concerning these diseases may well be due to the fact that it is incomplete.

SUMMARY

Ten cases are reported in which a common feature was myeloid hyperplasia.

Two cases were ordinary instances of leukemic myelosis, except that in the course of each there developed an almost completely aleukemic period. In one case the aleukemic period was thought to be due to irradiation of the spleen; in the other, it was "spontaneous."

Four cases thought to be diffuse hyperplasia of the myeloid tissue were characterized by severe anemia, leukopenia, a few abnormal leukocytes, secondary hemorrhagic purpura, changes in the bones and extramedullary collections of myeloid cells.

Two cases were indistinguishable from ordinary multiple myeloma, except that the tumors were made up of myeloid cells instead of plasma cells. One case presented chemical changes sometimes seen in multiple myeloma of the plasma cell type.

In the last two cases extramedullary myeloid tumors were present without definite evidence of disease of the bone marrow.

NOTE.—Since this manuscript was prepared, a boy, 10 years of age, with features similar to those in case 4 has been studied. The outstanding features were swollen gums, numbness of the chin and an osteolytic lesion of the mandible.

PERIPHERAL VASCULAR PHENOMENA

III. THE PERIPHERAL PULSE VOLUME IN OCCLUSIVE ARTERIAL DISEASES

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Early in the study of peripheral pulse volume by means of the plethysmometer described by Johnson,[1] it became evident that in persons suffering from occlusive disease of the arteries of the extremities, the pulse volume wave deviated sharply in size and contour from that obtained in normal persons. This change was found to be remarkably constant and could be repeated day after day, so that it was frequently possible to identify the patient by the appearance of the tracing (fig. 3). These changes were more uniform than were the deviations from the normal in persons with either valvular defect or myocardial impairment.[1]

It will be demonstrated that the character of the wave is not dependent on changes in the peripheral capillary bed, except that as in the normal state [1] and in Raynaud's disease the size of the wave diminishes with capillary and arteriolar vasoconstriction. Immediately after the induction of vasodilation by heat, the wave assumes a size and form which are uniform when the experiment is repeated under similar conditions, and they remain so until there has been an alteration in the occlusive pathologic process or a release of the angiospasm. Excursions of uniform maximum size for the subject and for the digit employed are the result. It is because of this constancy of observations that the method is offered as a diagnostic aid in the study of peripheral vascular disease.

Of the objective methods of study of these defects, it has been said that observations on the skin temperature are the most important. Certainly this method is most widely used both in the diagnosis of disease and in the differentiation between organic occlusion and vascular spasm. It is an indirect method, and the skin temperature is subject to many external variations such as room temperature, humidity and air currents,

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1. Johnson, C. A.: Studies on Peripheral Vascular Phenomena: I. A New Device for the Study of Peripheral Vascular Phenomena in Health and Disease, Surg., Gynec. & Obst. **55**:731 (Dec.) 1932.

2. Footnote 2 has been deleted by the author.

as well as many unknown variables, such as perspiration, heat radiation and fluctuations of the vasomotor system, all intangible and constantly varying in degree, so that the same conditions cannot be repeatedly imposed with certainty.

In addition to determining the condition of the larger vessels by palpation of the pulse in various locations and noting change in color with change in posture and the presence or absence of integrity of tissue, various other methods have been used or suggested. Oscillometric measurements, the histamine tests,[3] direct readings of the blood pressure in various arteries of extremities and the recent experimental observation of Allen and Camp on direct arteriography [4] have real value, but are either indirect or difficult of application.

The method here offered has most of the applications of the method in which the skin temperature is studied. It is a more direct measure of the circulation and can be used in the same manner as observations of the skin temperatures in the differentiation between organic and angiospastic obstruction to circulation. In addition, an objective permanent record is available.

METHOD OF STUDY

A simple plan was found to be adequate for the induction of standard conditions which resulted successfully in producing uniform results in each case: The patient is brought into the observation room, the temperature of which remains fairly constant, and is allowed to remain for a few minutes. Tracings of the pulse waves are then taken after observation of the surface temperatures. Tracings of the digits of the upper extremities are taken with the patient sitting comfortably in a chair with both arms resting on a table in such a manner as to secure complete relaxation with the hands at approximately the cardiac level. It is necessary to eliminate as much as possible the annoying element of tremor and somatic muscular movements which otherwise interrupt the smooth continuity of the tracing. The digits of the lower extremities are studied best with the patient in a recumbent position, although some of the records have been taken with the patient in the sitting posture. Tracings are then repeated immediately after the extremities have been immersed in water at 45 C. for ten minutes and rapidly dried. Observations have also been made after the induction of artificial fever by the injection of foreign protein and following ramisectomy and sympathetic ganglionectomy in one case previously reported.[5] The reflex effect of cold has also been determined, especially in Raynaud's disease and in thrombo-angiitis obliterans in which the clinical history has suggested undue vasoconstriction with cold.

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3. de Takáts, G.: Cutaneous Histamine Reaction as a Test for Collateral Circulation in the Extremities, Arch. Int. Med. **48**:769 (Nov.) 1931.

4. Allen, E. V., and Camp, J. D.: Roentgenography of the Arteries of the Extremities, Proc. Staff Meet., Mayo Clin. **7**:46:657 (Nov. 16) 1932.

5. Johnson, C. A.; Scupham, G. W., and Gilbert, N. C.: Studies on Peripheral Vascular Phenomena: II. Observation on Peripheral Circulatory Changes Following Unilateral Cervical Ganglionectomy and Ramisectomy, Surg., Gynec. & Obst. **55**:737 (Dec.) 1932.

The following are typical examples of peripheral arterial diseases of various types illustrating the deviation from the normal in the peripheral pulse volume wave in each instance.

REPORT OF CASES

CASE 1.—*Diabetic arteriosclerosis.*

B. D., aged 62, a Negress, entered St. Luke's Hospital in coma with severe diabetes. There was moderate sclerosis of the radial and brachial arteries but no impairment of circulation in the upper extremities. The left leg had been amputated previously because of diabetic gangrene. Circulatory impairment existed in the right foot; the dorsalis pedis and posterior tibial pulsations were not palpable; loss

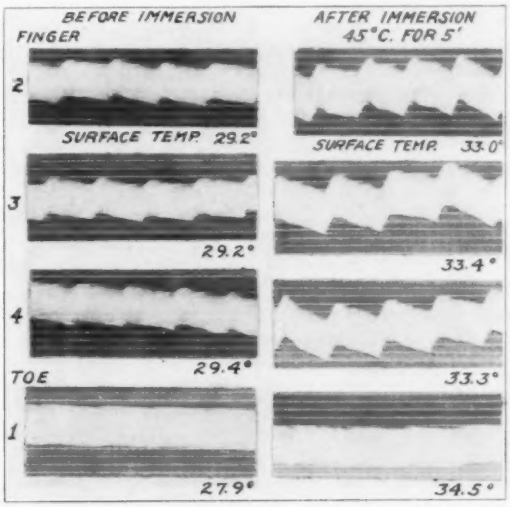

Fig. 1.—Tracings made from a patient with diabetic arteriosclerosis in whom gangrene developed four months later. The tracings are shown from the second, third and fourth fingers of the right hand with a normal response in these fingers before and after immersion in water at 45 C. for five minutes. In finger 3 the pulse volume is approximately 0.01 cc. before immersion, and 0.02 cc. following vasodilation of heat, showing a normal response in spite of an obvious arteriosclerosis. The lowest tracing shows the pulse volume of the right first toe with a very faint increase in volume before, and no significant change following, immersion. There were no subjective symptoms, although the other foot had been previously amputated for gangrene. The significance is evident. The space between the horizontal lines indicates 0.01 cc.

of heat was marked, and the foot was always cold. The surface temperature of the first toe averaged 27.9 C.

The tracing of the peripheral pulse volume (fig. 1) shows normal size of the wave in the right hand at room temperature with an average change in volume in the second finger of approximately 0.01 cc. After immersion in water at 45 C. for five minutes, this was increased to 0.02 cc. Similar changes occurred in all the

digits in the upper extremity. This constitutes a normal response and shows no impairment in circulation in spite of an obvious arteriosclerosis.

It will be noted that the pulse volume wave from the right foot is faint at room temperature and shows practically no change after induction of the vasodilation of heat. Subsequently, about four months later, gangrene developed in this foot, and amputation was necessary. Peripheral vasodilation failed to increase the size of the wave because obstruction in the larger arteries so limited the blood flow that the volume could not be increased in the capillary and arteriolar bed even with dilation. This demonstrates the findings of a severe degree of occlusion.

CASE 2.—*Senile arteriosclerosis with occlusion.*

J. S., aged 62, a white man, entered St. Luke's Hospital in the surgery A service of Dr. H. E. Jones. He had been having pain in the left foot for the past three years with some discoloration, and more recently, ulceration. He had had a previous infection of the toe of the same foot about five years before, but it had entirely healed. The pain was described as sharp and shooting, of from five to ten minutes' duration. This gradually became worse so that he had to use a cane. Then he began to have pain at rest, but change in the position of the foot gave some relief. Both feet were so susceptible to cold that it was difficult to keep them warm. The left foot became more discolored and painful. About three months before admission an ulcer appeared on the inner surface of the foot above the heel. This healed, but later opened again; since then the ulcer had increased in size.

The patient was a truck driver and had been a heavy smoker and drinker. He said that he had never had syphilis and that except for the complaints on entrance he had always been well.

Physical examination revealed moderate sclerosis and beading in all peripheral arteries, which were tortuous. The blood pressure was 140 systolic and 84 diastolic. The heart was normal except that there were frequent extrasystoles. The left foot had an ulcer on the medial aspect below the malleolus about 5 cm. in diameter with slightly raised edges of granulation tissue. There were two smaller ones above and anterior within 1.5 cm. of the larger one. Both feet were cold and showed dusky discoloration when dependent, with marked change to pallor when elevated. The dorsalis pedis and posterior tibial arteries could not be palpated in either foot. The femoral and popliteal pulsations were good. The veins seemed to be normal with no varicosities. The Kahn test was negative; renal function was unimpaired, and the blood showed no anemia. Observations on the skin temperature showed the hands to be warm, averaging about 34 C., with marked loss of heat in both feet; the temperature of the right first toe averaged 28.5 C., and that of the left, 27 C. The peripheral pulse waves in both hands were equal, and the right is shown in figure 2. It will be noted that there was a normal response at room temperature averaging 0.011 cc., with an increase to 0.022 cc. following immersion of the hand in water at 45 C. for ten minutes. Tracings of the first toe on both feet show no perceptible pulsation either before or after immersion in hot water. This would indicate a high degree of occlusion of the arteries of the feet and legs.

CASE 3.—*Thrombo-angiitis obliterans.*

P. C., aged 37, a white man, entered St. Luke's Hospital in the orthopedic service of Dr. Ryerson, complaining of pain in the right foot and leg. The first evidence of circulatory disturbance was three years before admission when he had pain in the left second finger. A small ulcer appeared, which finally healed. The finger became smaller at the end. While at work at the stockyards his duties took him to a cold storage room frequently. He noticed that ten minutes in the cold

room resulted in the right second finger turning white. There was no abrupt change to red afterward, but a return to normal color slowly. The pain stopped when he came back to a warm room. The ends of several fingers were successively involved. His feet began to trouble him about nine months before admis-

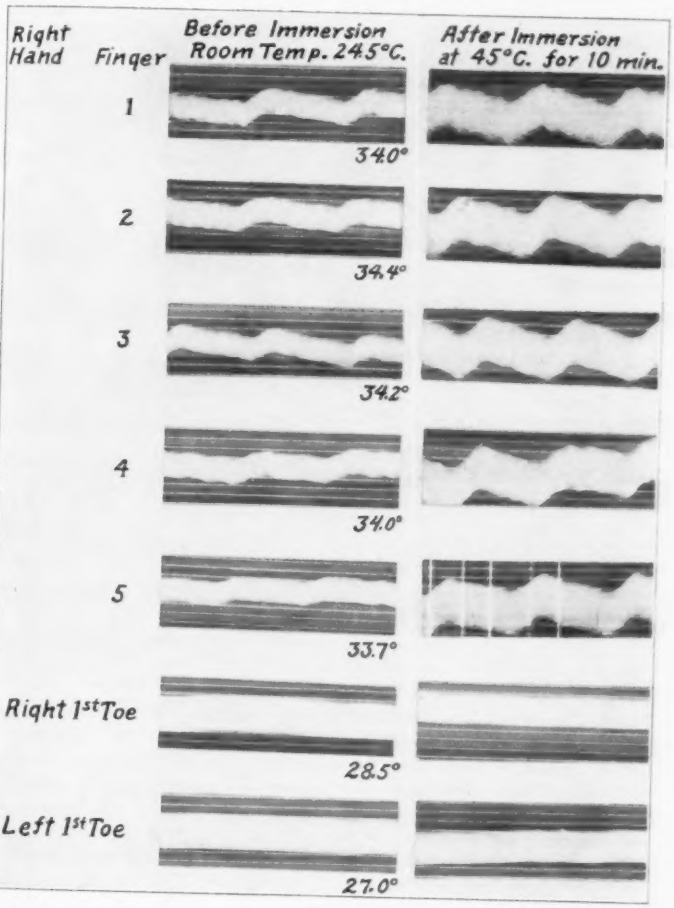

Fig. 2.—Tracings from a patient with senile arteriosclerosis with an ulcer on the left foot. There were no subjective symptoms in the right foot. The tracing of the peripheral pulse volume of the fingers of the right hand indicate unobstructed vessels. Tracings from the first toe of both feet show no pulse wave before, and no significant change following, vasodilation, indicating high grade occlusion. The skin temperatures are low.

sion. He would have pain in the region of the arch below the ankles if he walked about four blocks. He would then sit down and rest following which he could

walk again. Pain while resting began in the foot two or three weeks before admission. Since then he had been unable to stay in bed at night because of pain. His hands no longer caused any complaint.

He was a heavy smoker and drinker and smoked about from twenty to thirty handmade cigarets a day.

Examination showed a well developed, healthy appearing adult whose only pathologic findings were referable to the arteries of the hands and feet. There was apparent loss of heat in the right foot, which showed dependent rubor, and pallor on elevation. There was a gangrenous ulcer of the first toe. Most of the first phalanx was gone, and the bone was exposed. It was very tender and constantly painful. There were moderate swelling and redness and some evident secondary infection.

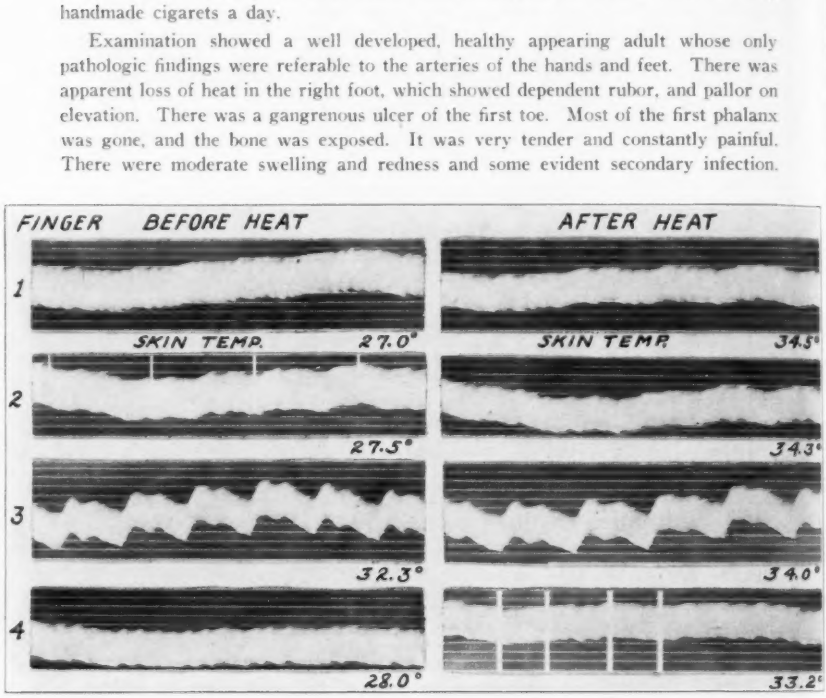

Fig. 3.—Tracings of a patient with thrombo-angiitis obliterans. The tracing of the right hand shows the pulse waves in fingers 1, 2, 3 and 4. There was past history of circulatory disturbance, but none at the time of the tracing. Fingers 1, 2 and 4 show definite evidence of occlusion with only a faint pulse wave before and after vasodilation by heat; no increase is noted. The irregular and frequent waves are due to tremor and somatic movement. Finger 3 shows a large pulse wave and a high skin temperature at room temperature and no appreciable increase following the vasodilation of heat, indicating a persistent vasodilation, a constant feature always noted in this case.

The dorsalis pedis and posterior tibial arteries were not palpable; the popliteal and femoral pulsations were normal. The left dorsalis pedis and posterior tibial arteries were palpable. The right radial artery was not palpable, but the ulnar was intact; the brachial artery seemed normal. The fingers of the right hand, except the third, were cold. The larger vessels in the left hand and arm were unimpaired.

The Wassermann reaction was negative. Renal function was normal. The blood showed no anemia, and viscosity was normal.

The peripheral pulse volume could not be determined in the right foot because of gangrene of the toe. In the left, it was unimpaired. The most interesting findings were demonstrable in the right hand (fig. 3). There were no perceptible pulse waves at room temperature except in the third finger in which the wave was maximum. The skin temperatures, it will be noted, were low in the first, second and fourth fingers, and in the third finger were nearly five degrees higher. After immersion of the hand in hot water at 45 C. for ten minutes, there was no essential change. A faint pulsation was noted in the first and second fingers, but this is questionable because of the small oscillations due to somatic tremor. In the third finger with a large pulse volume there was no increase in volume following vasodilation by heat, showing that the dilation of the capillaries and arterioles was complete and apparently fixed. This was a constant finding in this patient, and a similar condition has been noted in another case of thromo-angiitis obliterans. It is apparent that a persistent local vasodilation may occur in thrombo-angiitis obliterans and may account for the subjective sensations of heat and burning that are occasionally encountered in this disease, causing confusion with erythromelalgia, which has been noted.[6]

COMMENT

The pulse volume of a digit is shown by the height of the pulse wave in the tracing. It represents the increased amount of blood in the capillaries and the arterioles of the digit examined, resulting from systole of the left ventricle of the heart.[1] Conditions which modify the progress of blood through the arteries to the digit will conceivably modify the size of the wave, provided the heart is competent and has normal mechanism, and the pulse pressure is fairly well maintained. In the cases presented these factors were unimpaired.

The effects of external temperature and other stimuli on the capillaries and arterioles cause so much fluctuation in vasoconstriction and dilation by both direct and reflex action that full consideration of obstruction above the arteriolar level cannot be given to the findings unless there is certainty that the capillaries and arterioles are dilated and capable of responding to an uninterrupted blood flow. This is accomplished by immersion of the extremity in water at 45 C. for ten minutes, a procedure which eliminates the uncertainty of vasomotor activity for the period of observation.

If occlusion exists above the arteriolar level, the amount of blood delivered to the digit is diminished, and the size of the pulse wave varies with the degree of stenosis regardless of its location in the artery. The method as here described gives no indication of the location of the occluding process unless it can be demonstrated that the arteries at a certain level above are intact; then it may be assumed that the site is between that point and the digit examined. The presence

6. Brown, G. E.: Erythromelalgia and Other Disturbances in the Extremities Accompanied by Vasodilatation and Burning, Am. J. M. Sc. **183**:468 (April) 1932.

of an established collateral circulation does modify the findings. If it is entirely adequate, a normal response might be expected.

Angiospastic phenomena may be differentiated in this manner if the vasodilator stimulus of heat applied externally is of sufficient intensity. That this occurs is questionable in the case of spasm in larger vessels, such as the angiospasm occurring in Buerger's disease. That it occurs in the vasospastic phenomena of the smaller vessels is shown by the

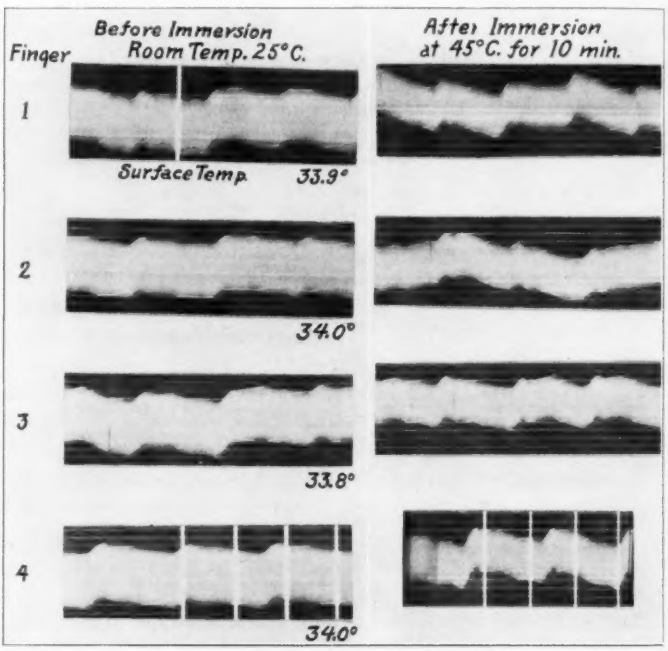

Fig. 4.—Tracings of four fingers of the right hand of a patient with thromboangiitis obliterans. No subjective symptoms were noted in the hands. Both legs were previously amputated. Normal pulse waves at room temperature with a normal response to heat are shown in fingers 1 and 4, but in 2 and 3 there is no increase in pulse wave. This is interpreted as evidence of a mild grade of impairment in the blood supply of these fingers.

fact that in Raynaud's disease the response to heat is a normal vasodilation, but with the stimulation by the proper degree of cold a prolonged vasoconstriction results, with a marked delay of the normal reactive peripheral vasodilation of the smallest vessels. Lower temperatures may result in a reactive vasodilation. These phenomena are discussed in a later communication.

That other stimuli do result in the release of spasm in the arteries may be demonstrated by figures 4 and 5, which represent the results of artificial fever in a case of thrombo-angiitis obliterans without marked involvement of the hands and without subjective symptoms referable to them. It will be noted that at room temperature there was a nearly normal pulse wave in the fingers of the left hand. Following the vasodilation of heat, there was a normal increase of pulse volume in fingers 1 and 4, but in fingers 2 and 3 there was no increase. The

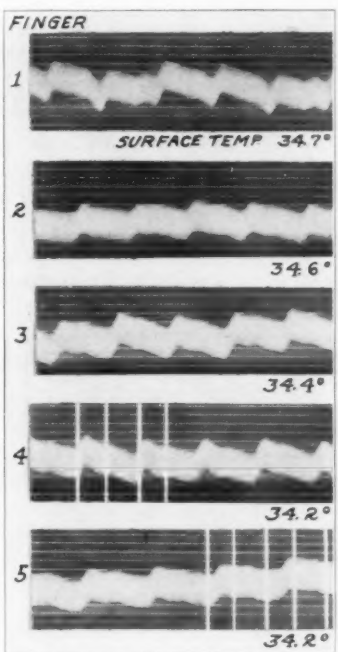

Fig. 5.—Same as figure 4 but following the artificial induction of fever without a significant fall in blood pressure. A small increase in pulse volume can be noted in finger 2 and very definite increase in finger 3, indicating the release of spasm not accomplished by immersion in hot water.

pulse waves were of about the same size, namely, about 0.008 cc. in both fingers before and after heat. This would indicate impairment of the circulation to these fingers, which probably existed in the smaller arteries of the digits themselves as the radial and ulnar arteries were intact. Following the induction of fever by intravenous injection of typhoid vaccine at an oral temperature of 101 F. (fig. 5), there was a definite increase of the pulse volume to 0.012 cc. in finger 2 and to

0.02 cc. in finger 3, indicating the release of spasm during fever. This interpretation is believed to be correct only if the pulse pressure is maintained and the heart is competent.[5] Other work, to be reported later, has led to the belief that an increase in peripheral pulse volume does not always occur with the artificial induction of fever, but may actually be diminished because of a coincident fall in blood pressure, or because of myocardial impairment with a fall in pulse pressure.

It may be noted here that in this patient, who had thrombo-angiitis obliterans of severe type which had resulted in the amputation of both legs several years previously, it was possible to demonstrate impairment of the efficiency of the circulation in the hands, although as yet there were no subjective symptoms and no demonstrable alterations in the skin temperature. It has been possible to demonstrate disease of the vessels in extremities other than the ones complained of in several instances, and it is believed in an early stage before the pathologic process had advanced to the degree from which there was ischemia sufficient to produce symptoms. This applies to thrombo-angiitis obliterans as well as to arteriosclerosis, and is particularly valuable in the determination of vascular efficiency in diabetes. Attention must be called to the fact that in size and contour the peripheral pulse wave in the lower extremities [1] differs from that noted in the upper, especially when tracings are taken with the patient in the sitting position. The wave is smaller and more sharply peaked.[1]

Observations on the differentiation of peripheral arterial spasm and occlusion by the nerve block method of Scott and Morton [7] and by the diagnostic blocking of sympathetic nerves [8] have been made. The method is applicable, as a marked temporary increase in pulse volume has been recorded immediately following sympathetic ganglionectomy, as reported in a previous paper.[5] The results with peripheral nerve block will be reported later.

Further observations on the effect of heat and cold stimuli on the capillaries and arterioles is in progress, but the essential observations necessary for the evaluation of the method in occlusive arterial diseases have been given.

SUMMARY

1. A method of study of the peripheral circulation has been applied to the diagnosis of peripheral vascular diseases.

7. Scott, W. J. M., and Morton, J. J.: The Differentiation of Peripheral Arterial Spasm and Occlusion in Ambulatory Patients, J. A. M. A. **97**:1212 (Oct. 24) 1931.

8. White, J. C.: Diagnostic Blocking of the Sympathetic Nerves to the Extremities with Procaine, J. A. M. A. **94**:1382 (May 3) 1930.

2. It is an objective method, more direct and in some respects more reliable than the determination of skin temperature. The procedure is simple and easy of application, and with it permanent records may be obtained for accurate subsequent comparison.

3. It is believed to be applicable, as a criterion, to all the methods for differential diagnosis between organic occlusion and angiospasm, in the same manner that determinations of skin temperature are now used.

4. It is valuable in the determination of occlusion in the smaller arteries of a digit when other methods are not applicable.

5. Mild degrees of partial occlusion in early cases in which skin temperatures show no reliable variation and in which subjective symptoms are confusing can be determined.

6. The method is simple and easy of application and interpretation.

LOBAR ATELECTASIS AS A CAUSE OF TRIANGULAR ROENTGEN SHADOWS IN BRONCHIECTASIS

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AND
DUNCAN GRAHAM, M.D.
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A few years ago we became interested in the occurrence of triangular basal shadows in roentgenograms of the chest of patients suffering from bronchiectasis. The first patient showing a triangular basal shadow discovered by one of us (W. P. W.) afforded an excellent opportunity for the investigation of the production of this type of shadow, as it was possible to study roentgenograms of the chest before and after the injection of iodized poppy seed oil 40 per cent into the bronchi, and later to remove the part of the lung causing the shadow and to observe its gross and microscopic appearance.

The shadows are seen as homogeneous areas of increased density, triangular in shape, with one side of the triangle along the mediastinum, the lower side parallel with the diaphragm and the hypotenuse running from near the root of the lung to join the lower side at varying distances from the mediastinum. If the shadow occurs on the left side, as in figure 1 *A*, it usually lies behind the cardiac shadow which, with the remaining structures in the mediastinum, is pulled toward the affected side. If the shadow occurs on the right side, the mediastinum is pulled toward the right. The diaphragm on the affected side is usually high.

Before discussing the results of our investigation regarding the significance and cause of the shadows, a brief review of the literature on the subject will be given. In 1925, Armand-Delille, Lévy and Marie,[1] in a paper on the use of iodized oil in the diagnosis of bronchiectasis in children, referred to the presence of triangular basal shadows in two of three cases, but did not comment on their significance. The same year, Comby,[2] in a discussion following a paper by Guinon and Levesque, stated that these roentgen shadows in children often

From the Department of Medicine, University of Toronto, and the Medical Service, Toronto General Hospital.

1. Armand-Delille, Lévy and Marie: Rev. franç. de pédiat. **1**:125, 1925.

2. Comby, J., in discussion on Guinon, L., and Levesque, J.: Sur les adénopathies trachéo-bronchiques non tuberculeuses; examen radiologique, Bull. Soc. de pédiat. de Paris **23**:151, 1925.

indicated bronchiectasis. In a roentgen study of bronchiectasis published in 1926, Singer and Graham [3] called attention to the triangular shadow densities in many cases of bronchiectasis, and stated:

> In the cases that have been operated upon, these triangular shadows have been found to represent atelectatic bronchiectatic lower lobes with the characteristic cyanotic appearance and indurated feeling on palpation. We have been surprised when the chest cavity was opened to find that the unaffected lobe or lobes had hypertrophied so much as to fill out the chest cavity and surround the collapsed lobe. In the roentgen plate these collapsed lobes manifest themselves as dense shadows in the region of the cardio-diaphragmatic region.

Injections of iodized oil were not used. In 1927, Rist, Jacob and Trocmé [4] investigated seven patients in whom roentgen films of the

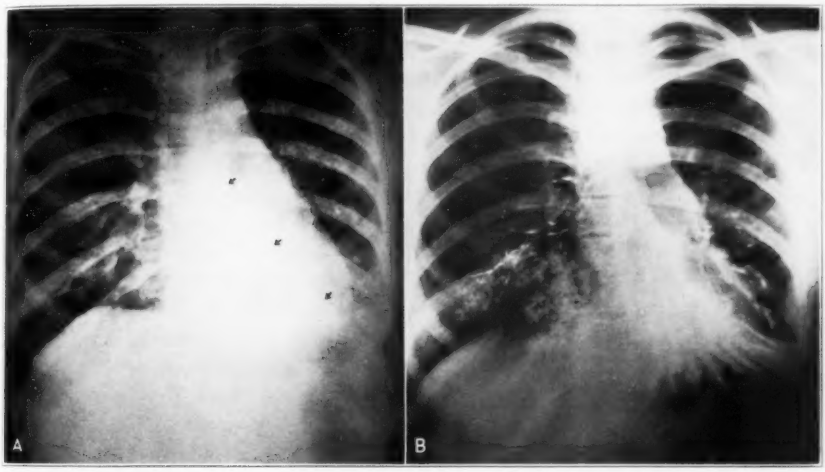

Fig. 1 (case 1).—*A*, a triangular shadow occurring on the left side, behind the shadow of the heart, which, with the remaining structures of the mediastinum, is pulled toward the affected side. *B*, appearance following the injection of iodized oil. The bronchi in the left lower lobe show cylindric dilatation.

chest showed triangular basal shadows. Previously these shadows were considered to be diagnostic of mediastinal pleurisy, but by injection of iodized oil, Rist and his co-workers were able to demonstrate the presence of bronchiectasis within the area of the triangular basal shadow. They came to the conclusion that the occurrence of these shadows was due in part to pleural thickening and in part to changes within the lung, both conditions developing secondarily to a primary bronchiectasis. Later in the same year these observations were con-

3. Singer and Graham: J. Missouri M. A. **19**:390, 1922.
4. Rist, Jacob and Trocmé: Ann. de méd. **21**:144, 1927.

firmed by Sergent and Bordet.[5] Wallgren,[6] in 1928, reported five cases of triangular basal shadows occurring in children and discussed their diagnostic significance. In the first case a right basal shadow disappeared after the removal of 20 cc. of fluid from the pleural cavity, and the shadow was considered to have been caused by a pleural effusion. Compression of the bronchus to the middle lobe by an enlarged gland produced atelectasis and caused the shadow in the second case. After two and one-half months the gland became smaller, the obstruction was removed, and the result was the re-aeration of the lobe and the disappearance of the shadow. The other three were cases of bronchiectasis in which there were histories of cough and expectoration of many years' duration. Wallgren noted that the heart was displaced to the side of the triangular shadow in the case of bronchiectasis, whereas in the case of pleural effusion it was displaced to the healthy side. In two cases he was able to show that the bronchiectasis was present for five years before the development of the triangular basal shadow. He considered that the changes within the lung, and not the thickening of the pleura, were the cause of the shadow.

In our study of bronchiectasis, particularly in reference to triangular basal shadows, we have endeavored to determine the significance and cause of the shadows, and have produced them experimentally. We believe that the work presented shows definitely the mechanism of their production and by so doing sheds considerable light on the problem of the cause of bronchiectasis. With the use of iodized oil injected into the bronchial tree, we were able to demonstrate that invariably these triangular shadows contain dilated bronchi. The bronchiectasis is usually cylindric (fig. 1 *B*), but occasionally saccular dilatations are present. The bronchi appear closely placed, with very little tissue between them, as compared with normal bronchi. That the triangular shadows contain bronchiectatic dilatations was also proved by bronchoscopic visualization and by examination of the surgically removed diseased area (lobectomy). We therefore feel that in any case in which a triangular shadow is present in a plain roentgen film of the chest, a tentative diagnosis of bronchiectasis is justifiable, and that the injection of iodized oil is indicated to confirm the diagnosis.

Not only have these triangular shadows invariably indicated the presence of bronchiectasis, but they have occurred frequently in the cases which we have studied. About 6 per cent of all our proved cases of bronchiectasis have shown them. They are therefore of definite diagnostic value, particularly in view of our difficulty in otherwise diag-

5. Sergent and Bordet: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:742, 1927.

6. Wallgren: Beitr. z. Klin. d. Tuberk. **69**:641, 1928.

nosing cases of bronchiectasis roentgenologically without the injection of iodized oil. This fact, along with the frequent occurrence of the shadows, makes them not a roentgen curiosity but a definite diagnostic aid. They have not received the attention which we believe their diagnostic value warrants.

Having become fully convinced of the diagnostic importance of the shadows, our next concern was the manner of their development. Obviously they were not due to dilated bronchi alone, as they were present in only 6 per cent of our cases. The injection of iodized oil into the bronchial tree gave the first indication of the nature of the shadows. By means of these injections the bronchi of the various lobes could be identified and a conception of the position and the size of the lobes obtained. It was found that if the triangular shadow was present on the left side, it invariably represented the left lower lobe. If it occurred on the right side, it represented either the right lower or the right lower and middle lobes. The lobes causing the shadow were much smaller than normal lobes. They had apparently left their normal position in the thorax, becoming greatly reduced in size and appearing as a uniform, dense shadow adjacent to the mediastinum. The upper lobes had enlarged and rotated so as to fill the space in the thorax normally occupied by the lower lobes. This is seen in figure 1 *B*, in which the main bronchus to the left lower lobe is seen to enter the triangular shadow and in which the branches are found only within the shadow. The bronchus to the left upper lobes is seen to supply the lung, occupying all the left side of the thorax except the triangular shadow. In stereoroentgenograms, branches of the bronchus of the upper lobe are seen in areas normally supplied by bronchi of the lower lobe. The lower lobe has therefore left the thoracic wall and a large portion of the diaphragm with which it is normally in contact and is now present as a small dense shadow behind the heart and close to the mediastinum. The remainder of the space which it normally occupied is filled with the expanded and rotated lobes. This conclusion was substantiated by bronchoscopic examination and later by direct observation on opening the thorax surgically in order to remove the bronchiectatic lobe. Similarly, if the shadow is situated on the right side, it could be shown to represent either the right lower lobe or the right middle and lower lobes, greatly reduced in size. In right-sided triangular shadows, therefore, the upper and middle lobes or the upper lobe alone expanded to fill the thorax.

The next problem was to determine the cause of the decrease in the size of the affected lobes. In this connection we were fortunate in being able to observe a case of bronchiectasis of recent origin (about four months) with disease in the left lower lobe. This lower lobe was represented by a triangular shadow (fig. 1 *A*) and was removed by

open operation through the wall of the chest. A brief summary of the clinical findings and the investigation of the case follows:

CASE 1.—Mrs. V. W., aged 23, was admitted to the medical service of the Toronto General Hospital on Feb. 17, 1930. She stated that she was perfectly well until three and one-half months before admission, at which time a dry cough with practically no expectoration developed. Two weeks later she acquired a severe cold in the head; the cough increased, and she began to expectorate about 2 ounces a day of a greenish material. One and one-half months before admission a sharp, severe pain developed in the left side of the chest anteriorly, just below and to the outer side of the heart. She felt quite ill at this time but was in bed only three days. However, she continued to lose weight and to feel ill, and the cough and the expectoration persisted. During the three and one-half months of her illness she lost 25 pounds (11.3 Kg.). She did not feel well for the first two months of her illness. At the time of admission she felt well, her only complaint being cough with about an ounce of greenish-yellow sputum which at no time had a foul odor.

Examination.—The patient did not look ill, and there was no clubbing of the fingers. The left side of chest moved less than the right. At the back on the left side a triangular area of dulness could be made out on percussion. Over this area were bronchial breath sounds, crackling medium râles and whispered bronchophony. Repeated examinations of the sputum for tubercle bacilli gave negative results. Roentgen examination (fig. 1*A*) showed a normal right lung and left apex with a triangular basal shadow behind the shadow of the heart. A tentative diagnosis of a bronchiectatic left lower lobe was made. Local pleural or mediastinal effusion was ruled out by aspiration.

Iodized oil was then injected by the supraglottic route into the left side, and it was seen (fig. 1*B*) that the main bronchus to the left lower lobe went to the triangular shadow, and that the bronchi in it showed cylindric dilatations. The bronchi appeared quite close together, and one was able to state from the picture after the injection of the iodized oil that the triangular shadow represented the complete left lower lobe, which was about the size of the clenched fist. The left upper lobe had become enlarged and rotated so as to fill the space normally occupied by the lower lobe. This could definitely be determined by making injections into the bronchus to the left upper lobe. The bronchi of the upper lobe were seen in areas normally occupied by the lower lobe. The bronchi in this lobe were normal except for a small strip at the lower edge parallel to the lower lobe, which showed cylindric dilatation.

The final diagnosis of an atelectatic, bronchiectatic left lower lobe was made. A small strip of bronchiectasis was thought to be present at the edge of the left upper lobe. Pneumectomy was considered advisable, and, after a preliminary phrenectomy, the left side of the thorax was opened by Dr. Norman Shenstone and Dr. Robert Janes. No pleural adhesions were found. The left lower lobe was completely collapsed; it had no thickened pleura and did not appear at all like a fibrosed lobe but like an atelectatic one. There was an area along the lower edge of the upper lobe which also looked atelectatic. The left lower lobe, as well as the collapsed portion of the upper lobe, was removed.

The pathologic report of the surgical specimen was made by Dr. W. L. Robinson of the department of pathology.

The gross specimen consisted of a wedge-shaped, soft, rubbery lobe of pulmonary tissue measuring 14 by 9.5 by 2 cm. The bronchi were thick-walled and

dilated to within 2 mm. of the pleural surfaces. Sections of the upper lobe revealed similarly thickened bronchi which presented, however, less dilatation.

Microscopically, sections of the bronchi showed that many of the lumens were almost completely filled with fibrinopurulent exudate. Polymorphonuclears were seen throughout between the lining cells of the mucosa. The epithelial lining was for the most part heaped up and redundant in appearance. Occasional small areas of ulceration were noted. Immediately beneath the epithelium was a fairly broad zone of lymphocytic and plasma cell infiltration in which numerous small congested capillary vessels were seen. A few eosinophils were noted. The peripheral portions of the bronchi showed a well established fibrosis. The cartilaginous plates were embedded in an unusually dense fibrous tissue and showed slight degenerative changes and irregularity in the cellular arrangement. The adjacent pulmonary parenchyma showed a definite collapse, the alveoli of which were lined with a continuous layer of cuboidal epithelium. Elsewhere in a few areas there was fibrosis of the pulmonary parenchyma, in which irregular outlines of alveoli were noticed. The bronchial arteries of the specimen were all thick-walled. Sections of the upper lobe showed a similar picture. It should be noted that the cilia of the mucosal epithelium of the bronchi could easily be identified in the hematoxylin-eosin section. Sections stained for bacteria and for spirochetes were negative.

It is obvious that in this case the bronchiectatic left lower lobe was small and produced a triangular shadow in a roentgenogram because it was atelectatic. There was no pleural thickening and practically no fibrosis of the parenchyma. The triangular shadow in this case was due to an atelectatic or collapsed lower lobe, the bronchi of which were bronchiectatic. It could be seen at operation that the greater part of the space normally occupied by the lower lobe was filled by the expanded upper lobe.

The cause of this atelectasis of the lower lobe was at first obscure. It could not have been due to plugging of the bronchi by secretion, because from the time the patient first came under observation until operation the atelectatic bronchiectatic lobe gave all the physical findings of consolidation with patent bronchi, and the bronchi could be filled by iodized oil. The bronchi appeared patent also at operation, and showed very little secretion. From these findings it was obvious that the atelectasis was probably due to distal obstruction of the bronchi. Careful search was made of the microscopic sections of the lung, and it was seen (figs. 2 and 3) that the terminal bronchioles were closed or practically closed by inflammatory swelling of the bronchial wall. We therefore had the probable cause of the atelectasis of the bronchiectatic lobe.

Besides this direct proof that atelectasis may cause the small lobe producing the triangular shadow, we observed a shadow that appeared and changed in size so rapidly that atelectasis seemed the only possible explanation. A brief outline of the history of the patient in whom this was observed is as follows:

Case 2.—Miss M. C. S., aged 30, was first seen by us when she was admitted to the Toronto General Hospital on July 3, 1931, almost three months after the

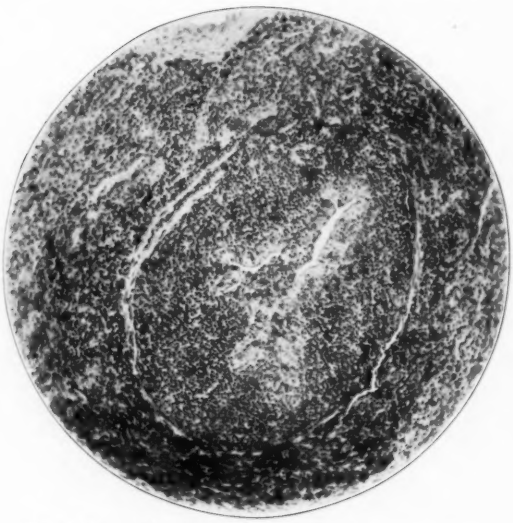

Fig. 2 (case 1).—Microscopic section of the lung.

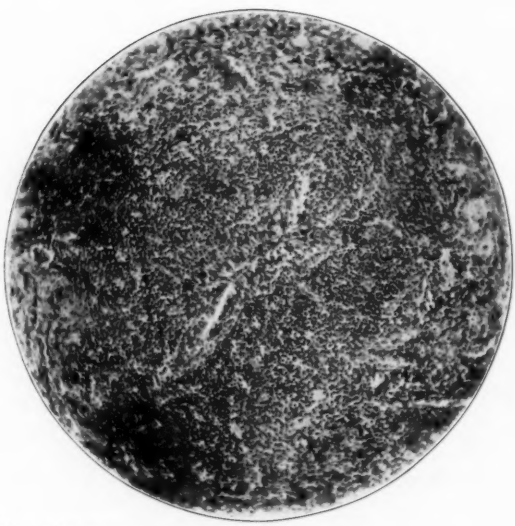

Fig. 3 (case 1).—Another microscopic section, showing the same features as figure 2.

onset of her illness. She gave a long history of cough with slight sputum. This began when she was a child and continued until 1926, when she was 25 years of age. During this time she had considerable nasal and postnasal discharge. In 1926, she had a tonsillectomy, and a bilateral intranasal antral operation was performed. Following these procedures, the cough and the sputum entirely disappeared, and she had no symptoms for five years. At the end of this time, in April, 1931, she had a sudden, sharp pain on the left side of the chest and became quite ill with what was thought to be bronchopneumonia and fibrinous pleurisy on that side. She had a prolonged illness with continual cough and purulent expectoration, and physical findings persisting at the base of the left lung. A diagnosis of bronchiectasis was made by her physician.

Physical examination at this time showed a patient not in good health. She had a slight cough with about 2 ounces a day of purulent sputum which was not foul. The left side of the thorax was restricted in movement, and at the base of the left lung posteriorly there were medium crackling râles. Over this area breath sounds were harsh and bronchovesicular, and whispered voice slightly increased. The right lung showed no abnormal findings. The sputum was repeatedly negative for tubercle bacilli.

Stereoscopic roentgen films of the chest showed heavy bronchial markings at the base of the left lung; the mediastinum was in the midline. The right lung as well as both apexes appeared clear. Iodized oil was injected into the base of the left lung by the supraglottic route, and the roentgenogram (fig. 4*A*) showed cylindric bronchiectatic dilatation at the base of the left lung. Some of the iodized oil entered the base of the right lung where the bronchi appeared to be normal. A subsequent injection of iodized oil into the right lung revealed no evidence of bronchiectasis. These examinations were made on July 10 and July 12.

The diagnosis of left-sided bronchiectasis was thus confirmed, and the patient was sent back to her home for a month of further convalescence before returning for a left lower lobectomy.

She returned for the operation on August 14. Physical examination at this time gave results identical with those obtained in July. There were no abnormal physical findings in the right side of the chest; the mediastinum was in the midline. On August 17, Shenstone and Janes performed a partial pneumectomy (lobectomy of the left lower lobe). This was preceded by a preliminary phrenectomy. Following the removal of the left lower lobe, a complicating effusion developed on the left side. The effusion was never extensive, and continuous suction drainage of the left pleural space was kept up.

On August 22, it was noted that there was impaired resonance at the base of the right lung, with medium râles and rhonchi. On August 25, eight days after operation, impaired resonance, bronchial breath sounds and crackling râles were found posteriorly on the right side. At this time a portable roentgenogram was taken of the chest, which showed a triangular shadow at the base of the right lung. Instead of finding the mediastinum shifted to the side on which the operation occurred (the left in this case), as is usual following lobectomy, it was shifted to the right side. On September 5, the patient was doing fairly well except that she was coughing up about 3 ounces of purulent sputum a day. On examining the right side of the chest posteriorly, a definite triangular area of impaired resonance, bronchial breath sounds, crackling râles and bronchophony were made out. The triangular area was along the vertebral column, reaching farthest from it at the level of the diaphragm. The mediastinum was shifted to the right side. A roentgenogram (fig. 4*B*) taken on September 5 showed a distinct triangular basal shadow on the right side corresponding in position to the area over which the

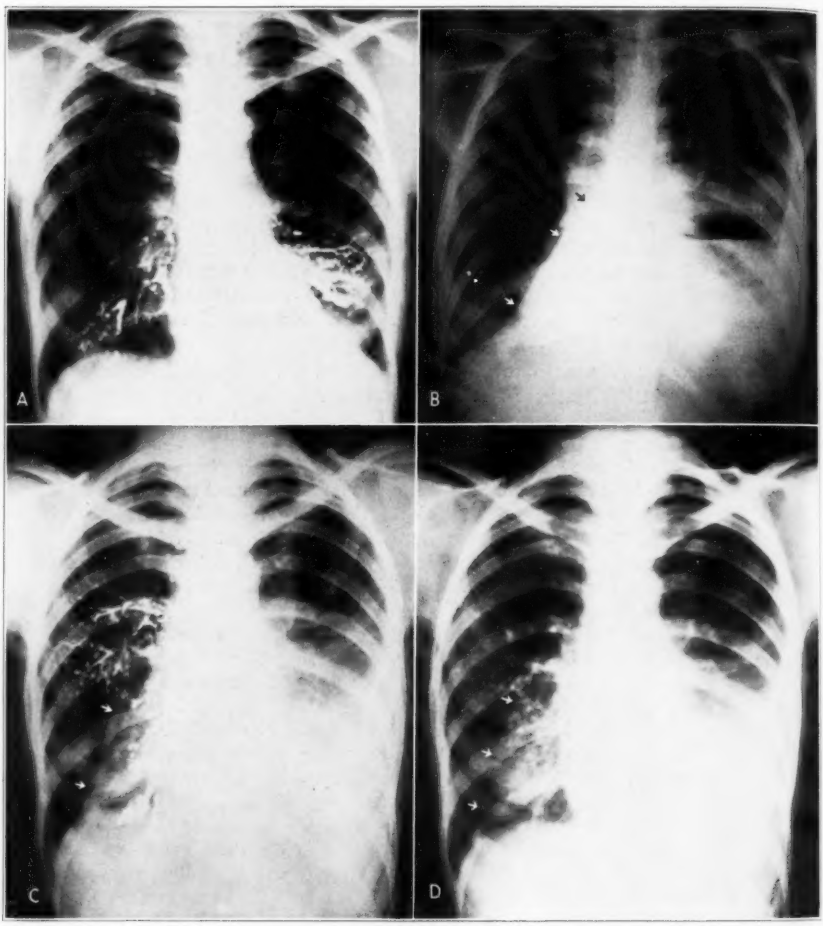

Fig. 4 (case 2).—*A*, a stereoscopic roentgen film showing cylindric bronchiectatic dilatation at the base of the left lung. *B* shows a distinct, triangular basal shadow on the right side corresponding in position to the area over which impaired resonance, bronchial breath sounds, crackling râles and bronchophony were noted. The mediastinum was shifted definitely to the right at this time (Sept. 5, 1931). *C*, a roentgenogram taken after a supraglottic injection of iodized oil. In the triangular basal shadow the bronchi are seen to be close together and to show cylindric dilatations. *D*, a roentgen film taken on Oct. 17, 1931, showing a much larger and less distinct triangular arc. The mediastinum has definitely moved back toward the midline.

aforementioned physical findings were elicited. The mediastinum was shifted definitely to the right. On September 19, the patient was still expectorating 3 ounces of purulent sputum a day. Physical signs over the lower part of the right side of chest were not so marked as on September 5. Roentgenograms still showed the triangular shadow plainly but slightly increased in size and not so homogeneous. On October 5, a roentgenogram showed the triangular shadow definitely larger than did the previous film. It was decided to inject iodized oil into this basal shadow. This was done by the supraglottic route, and figure 4*C* shows a roentgenogram taken following the injection. The iodized oil entered the triangular shadow, the bronchi of which were seen to be close together and to show cylindric dilatations. On October 17, the patient was doing well; however,

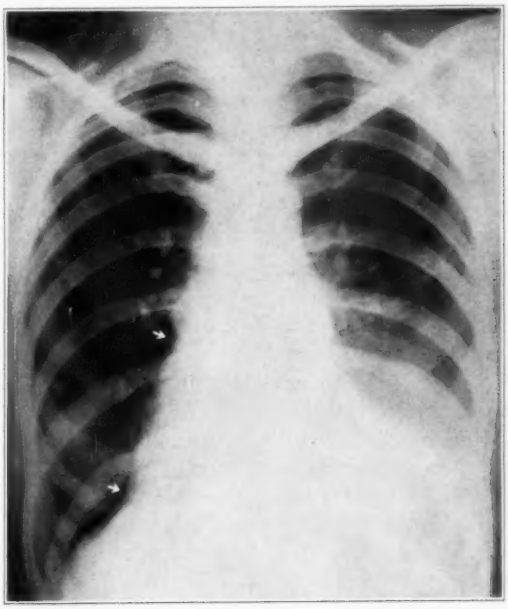

Fig. 5 (case 2).—A roentgenogram taken on Feb. 15, 1932, showing a distinct triangular basal shadow and the mediastinum again placed over toward the right. The triangular shadow is dense, small and homogeneous, and similar to that seen on September 5.

the expectoration of 2 ounces of purulent sputum a day persisted. Examination of the right side of the chest now showed few physical signs. The only remaining abnormal finding was a few medium râles. It was no longer possible to outline the triangular area clinically. Roentgen examination showed that the triangular area was much bigger and less distinct, and that it tended to be less easily differentiated from the surrounding lung (fig. 4*D*). The mediastinum had definitely moved back toward the midline. Further, iodized oil injected at this time into the bronchi of the right lung demonstrated that the triangular shadow was caused by a small right lower lobe. It could be seen that the right middle and upper lobes

had enlarged and rotated so as to fill the space in the thorax normally occupied by the lower lobe. The patient improved in general health and was allowed to go home to continue postural drainage, which had been started as soon as she was well enough following the lobectomy. On discharge, she had slightly purulent sputum. This continued with occasional blood-streaking until she returned for examination on Feb. 15, 1932. She had felt quite well in the interval and had gained definitely in strength and weight. A roentgen film (fig. 5) taken at this time showed the triangular basal shadow distinctly; the mediastinum was again seen toward the right. The triangular shadow was dense, small and homogeneous, and appeared similar to the shadow seen on September 5. Iodized oil injected into the right lung again demonstrated bronchiectasis in this area, recognized as the right lower lobe.

It is seen in this case that a triangular basal shadow, representing a bronchiectatic lobe, developed in a patient known to have had bronchi of normal size six weeks previously. The right lower lobe had become bronchiectatic and so greatly reduced in size that it gave a triangular-shaped shadow on the roentgenogram. The lobe then enlarged to over twice this size in a period of only six weeks, returning to the small triangular shape during the following three months. It is inconceivable that fibrosis of the lung or a pull by contracting pleural adhesions could cause such a sudden decrease in size. The rapid expansion that took place after the small lobe was present for a few weeks could not have taken place if fibrosis had been the cause of the reduced bulk. The lobe must have decreased in size, owing to the atelectasis, which partially cleared and then returned.

It is also of interest to note that in both cases presented the atelectatic, bronchiectatic lobe was recognized clinically as a triangular area of dulness along the spinal column. In only a small percentage of cases is one able to outline the lobe clinically, but when this is possible, one finds, in addition to impaired resonance, all the other signs of consolidation, i. e., bronchial breath sounds, bronchophony and medium crackling râles. Very often, when the roentgen ray reveals a triangular shadow, one is unable to outline it clinically. A different set of physical findings produced because of atelectasis of a lobe is well illustrated by a case in which the left lower lobe was so small that it was represented by a shadow only at the hilus (fig. 6 *A*). The lobe had left the diaphragm altogether and was therefore not in the shape of a triangle. The physical findings were definitely different in the two sides of the chest. The left lower lobe was centrally placed and so small that it was impossible to find it clinically, but, owing to the overstretched upper lobe, one noted the physical signs of a one-sided emphysema. That is, the left side gave a boxy, hyperresonant note on percussion; the breath sounds on that side were typical of emphysema, while the right side of the chest appeared normal. This case presented the smallest lobe that we have seen. Figure 6 *B* represents a roentgenogram taken after the injection of iodized oil in this case. The closely

placed, dilated bronchi are seen in the shadow near the hilus. Some of the iodized oil has entered the upper lobe, and the bronchi arising from its main bronchus are seen to go to the base in an area usually supplied by the bronchi of the lower lobe. In this particular instance, both the injection of iodized oil and the bronchoscopic examination, proved that the shadow was due to the entire left lower lobe.

As far as we are aware, no occurrence of bilateral triangular shadow in bronchiectasis has heretofore been reported. We have observed two cases showing bilateral shadows. In one, the plain roentgen appearance is shown (fig. 7 *A*). With an injection of iodized oil, the left lower

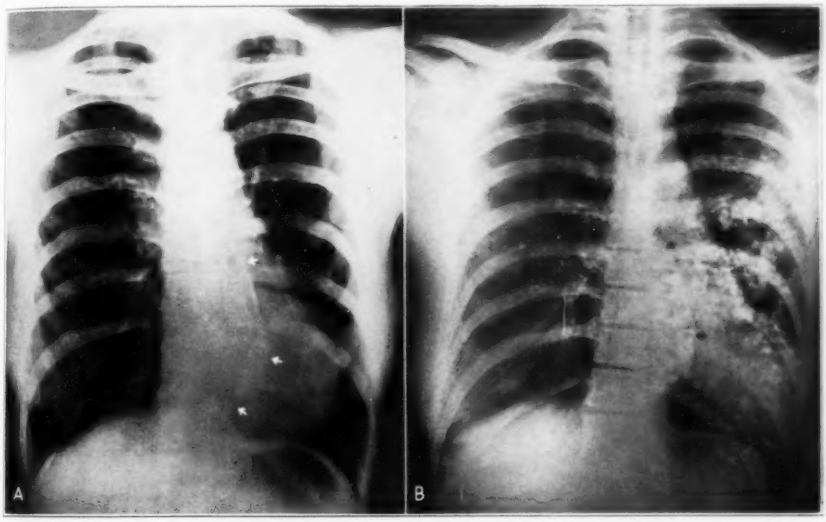

Fig. 6.—*A*, a case of atelectasis of a lobe in which the left lower lobe was so small that it was represented by a shadow only at the hilus. *B*, the same as *A*, after injection of iodized oil. The closely placed, dilated bronchi are seen in the shadow near the hilus. Some of the oil has entered the upper lobe, and the bronchi arising from its main bronchus are seen to go to the base in an area usually supplied by the bronchi of the lower lobe.

lobe was seen as a triangular shadow, the left upper lobe filling the remainder of the left hemithorax. On the right side, the right lower lobe produced the shadow, and the remainder of the right hemithorax was occupied by the right middle and upper lobes (fig. 7 *B*). In the other case of bilateral basal triangular shadow, the left-sided shadow was due to the left lower lobe, whereas the right was due to the right lower and middle lobes (fig. 8). In this case the two upper lobes were the only lobes expanded and aerated.

LOBAR ATELECTASIS, EXPERIMENTALLY PRODUCED IN DOGS, CAUSING A TRIANGULAR BASAL SHADOW

If, as it seemed proved, atelectasis of a lower lobe caused the lobe to become small, triangular in shape and situated as we saw it in our roentgenograms, it should be possible to reproduce the shadow in animals by causing atelectasis of the lower lobe.

In dogs, with the cooperation of Dr. Gregor McGregor of the Department of Otolaryngology, we were able completely to occlude the bronchus to a lower lobe by means of a balloon inserted through a bronchoscope. The deflated balloon was inserted and then blown up

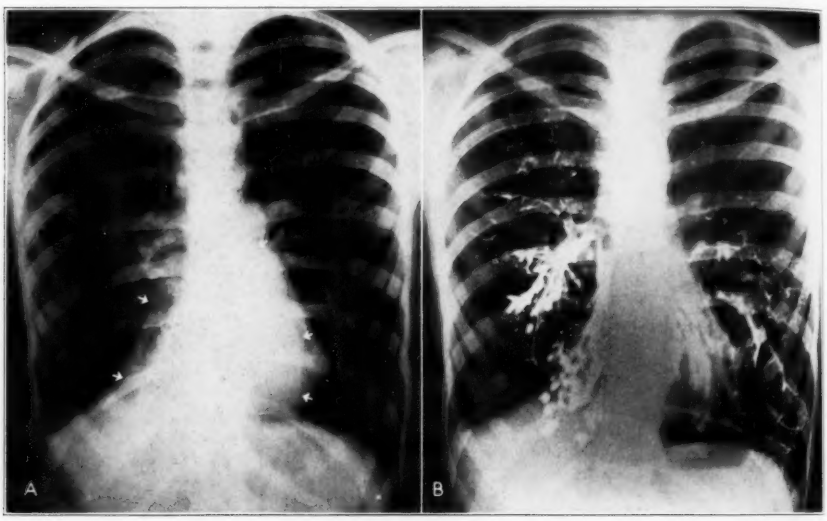

Fig. 7.—*A*, a roentgenogram showing a bilateral triangular shadow in bronchiectasis. No other instances of this condition have heretofore been reported. *B*, appearance after the injection of iodized oil. The left lower lobe is seen as a triangular shadow, the left upper lobe filling the remainder of the left hemithorax. On the right side, the right lower lobe produced the shadow, and the remainder of the right hemithorax is occupied by the right middle and the upper lobes.

so that it occluded completely the lumen of the bronchus. We found it technically very difficult to occlude the bronchus completely by means of an apparatus inserted through a bronchoscope. However, a balloon was made by which we were able to do this with regularity. Roentgenograms were made of the chests of the dogs, and under anesthesia the balloon was inserted into the bronchus to the lower lobe. The dog was allowed to come out of the anesthesia and, in the majority of cases, showed few signs of distress. At the end of twenty-four hours

the dog was again examined by roentgen rays, and in all cases in which the balloon completely occluded the bronchus of the lower lobe, a typical triangular basal shadow was seen on that side. The roentgenologic appearance of the chest was similar to that seen when a triangular basal shadow is present in man (fig. 9). The shadow itself was similar in shape and position; the mediastinum was shifted to the affected side, and the diaphragm on that side was elevated in the thorax. This appearance was present twenty-four hours after the obstruction was produced. If the animal was killed after this amount of time had

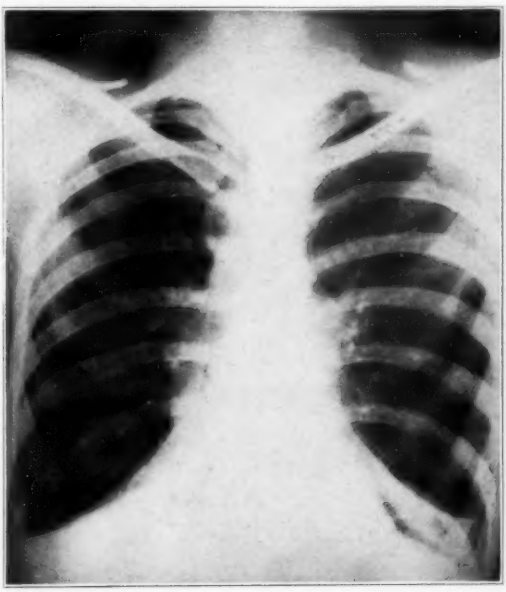

Fig. 8.—In this second case of bilateral triangular shadow, the left-sided shadow was due to the left lower lobe, whereas the right-sided shadow was due to the right lower and middle lobes. In this case the two upper lobes were the only lobes expanded and aerated.

elapsed, an atelectatic lobe was found situated in the thorax in such a position that it undoubtedly caused the triangular shadow. We were also able to remove the balloon from the bronchus through a bronchoscope at the end of twenty-four hours, after it had produced an atelectatic lobe giving a triangular shadow in the roentgenogram of the chest. Within five minutes after removing the obstruction, the lobe was seen under the fluoroscope to expand with each inspiration and to become indistinguishable from the rest of the lung. With this disappearance

of the triangular shadow, the diaphragm and mediastinum returned to their normal positions.

We were thus able to produce in dogs triangular shadows with shifted mediastinums and high diaphragms. This was done by causing atelectasis or deflation of a lower lobe by obstructing the bronchus to that lobe. The roentgenologic appearance was identical with that observed in human beings having bronchiectasis with triangular shadows. The technic employed in these experiments is not given, but

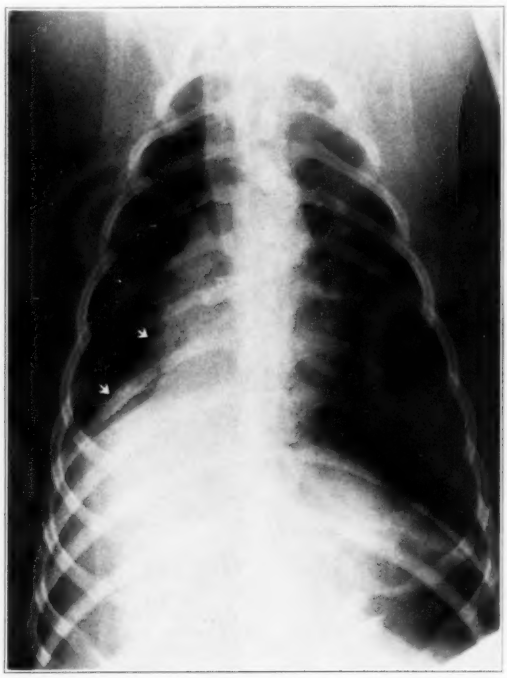

Fig. 9.—Roentgen appearance of the chest of a dog when a triangular basal shadow was created by the insertion of a balloon into the bronchus of the lower lobe.

it will be reported later when further work now being carried out on the experimental study of bronchiectasis is reported.

COMMENT

We believe that triangular basal shadows as described always indicate bronchiectatic lobes. Their presence in a roentgenogram of the chest warrants a provisional diagnosis of bronchiectasis, and iodized oil

should be injected to confirm this diagnosis. In every case in which one of the shadows has occurred, we have been able to prove that bronchiectasis was present. Other roentgen ray evidence of bronchiectasis is so unsatisfactory that we believe that, apart from the injection of iodized oil, triangular shadows are the best evidence of bronchiectasis that occur in plain roentgen films of the chest. They also occur frequently enough (6 per cent of our cases) to make them of real diagnostic value.

It has been shown that triangular basal shadows may be caused by atelectasis of the bronchiectatic lobe—lobar bronchiectasis—without significant fibrosis of the parenchyma of the lung or thickening of the pleura. Occlusion of the terminal bronchioles in the affected lobe from inflammatory exudate in their walls would appear to be the immediate cause of the atelectasis. It is possible for the atelectatic lobe to leave the wall of the chest and part of the diaphragm without the presence of any substance, such as air or fluid, in the pleural cavity. As the lobe becomes small and atelectatic and takes up its new position, the upper lobe expands to fill the place that it formerly occupied in the thorax. It seems unlikely that fibrosis or pleural contraction can cause the lobe to shrink and assume the shape which throws a triangular shadow on the roentgen film. If fibrosis could cause this change, one would expect to find the shadows quite frequently in a fibrosing disease, such as chronic pulmonary tuberculosis. We have not observed them in this disease. Contraction of pleural adhesions might cause the mediastinum to shift and the wall of the chest to move in. However, the lobe would be adherent to the wall of the chest and the diaphragm and could not detach itself from these and move toward the hilus. We therefore believe that atelectasis must always be the initial cause of the smallness of the lobe. Where infection occurs through the entire thickness of the walls of the bronchi in bronchiectasis, it is obvious that the infection will spread in time to the collapsed or atelectatic alveoli and may lead to fibrosis of the parenchyma, with or without pleural thickening and adhesions.

Since the time of Corrigan [7] and Hamilton [8] there have been many adherents to their theory that bronchiectasis is primarily a disease of the parenchyma, and that the bronchi are caused to dilate by the direct pull of fibrous tissue occurring in it. Sergent,[5] in discussing triangular basal shadows and their relationship to bronchiectasis, favored this view. We believe that the theory first advanced by Andral [9] and later

7. Corrigan: Dublin M. J. **13**:270, 1838.

8. Hamilton: Practitioner **22**:426, 1879.

9. Andral: Clin. méd., Paris **2**:22, 1824.

by Stokes,[10] that the bronchus is the structure primarily at fault in bronchiectasis, is substantiated by our observations that bronchiectasis may develop without fibrosis of the lung or pleural adhesions being present. There is ample evidence to show that in bronchiectasis the wall of the bronchus is weakened by destruction of its elastic and muscular coats.[11] The normal dilating force of respiration acting on the infected and weakened wall of the bronchus is probably the chief cause of the permanent dilatation found in bronchiectasis.[12]

CONCLUSIONS

1. Triangular basal shadows as seen in roentgenograms of the chest are diagnostic of bronchiectasis. Their presence should always be taken as an indication for the injection of iodized oil to confirm this diagnosis.

2. They occurred in about 6 per cent of all our cases of bronchiectasis.

3. Two cases of bilateral triangular basal shadows are reported.

4. Triangular basal shadows are caused in some cases at least, and probably in all cases initially, by a lobar atelectasis of the brochiectatic lobe.

5. We believe that the cause of this lobar atelectasis is the plugging of the terminal bronchioles by the swelling of the bronchial wall with an inflammatory exudate.

6. Lobar atelectasis produced in dogs by completely occluding the bronchi of the lower lobes caused typical triangular shadows due to the atelectatic lower lobe.

7. Atelectatic bronchiectatic lobes may occasionally be found on physical examination; such physical findings are diagnostic of bronchiectasis.

8. Bronchiectasis may occur in the absence of both fibrosis of the pulmonary parenchyma and pleural adhesions.

Various departments aided in this work. Dr. Gregor McGregor, of the department of otolaryngology, and Dr. A. C. Singleton, of the department of radiology, were of particular assistance.

10. Stokes, William: A Treatise on the Diagnosis and Treatment of Diseases of the Chest, Dublin, Hodges & Smith, 1837.

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INTRA-UTERINE RHEUMATIC HEART DISEASE

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Intra-uterine rheumatic fever is so rare that it is considered a historical curiosity,[1] and Abbott,[2] though she was of the opinion that rheumatic endocarditis might be transmitted from the mother to the embryo, mentioned that up to the present time there is no direct proof.

In 1882, Pocock [3] described a case of rheumatic fever in a new-born, premature infant, whose mother was suffering from the same infection at the time of delivery. Thirty hours after birth the infant disclosed symptoms which led to a prompt diagnosis and treatment with sodium salicylate. The child recovered, and mention is made that there was no detectable damage to the heart.

In the case reported by Schaefer,[4] in 1886, the mother had rheumatic fever five days prior to delivery. When the child was 3 days old, it also had rheumatic fever which persisted for two months and followed a typical course. The child was treated with salicylates, and no cardiac damage was noted.

In 1888, Guthrie [5] reported a case in which the mother showed symptoms of rheumatic fever three days after delivery, and the child, when it was 11 days old. The joints were reddened and swollen and yielded to treatment with alkalis. There was no mention of the condition of the heart.

In the case described by Ferguson,[6] in 1893, the mother suffered a severe attack of rheumatic fever which persisted from the second

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From the Departments of Cardiology, White Cross Hospital and Children's Hospital.

1. Torry, R. G.; in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc., 1927, vol. 2, chap. 4, p. 596.

2. Abbott, Maud E., in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1929, vol. 4, chapt. 4, part 2, p. 220.

3. Pocock, F. E.: A Case of Acute Rheumatism Occurring in a Newly Born Infant, Treated with Salicylate of Soda, Lancet **2**:804 (Nov. 11) 1882.

4. Schaefer: Ein Fall von acutem Gelenkrheumatismus bei einer Mutter und deren neugeborenem Kinde, Berl. klin. Wchnschr. **23**:79 (Feb. 1) 1886.

5. Guthrie, A.: A Case of Acute Rheumatism in an Infant Eleven Days Old, M. Prog. **10**:746 (June 16) 1888.

6. Ferguson, J. H.: A Case of Intrauterine Rheumatism, Edinburgh Hosp. Rep. **1**:608, 1893.

month of her pregnancy until delivery. She gave birth to a living child apparently suffering from rheumatic fever. This diagnosis was made because of the maternal history, the distressing cry of the infant on being moved and the characteristic temperature curve. Postmortem examination revealed the heart to be normal.

REPORT OF A CASE

History.—The mother had had recurrent attacks of rheumatic fever since she was 12 years of age. Eight years following the onset, she suffered a severe attack during which she was told that she had heart disease. At the age of 25 she became pregnant and gave birth to the patient, a full-term boy. Throughout this entire pregnancy and at the time of delivery the mother had active rheumatic fever with an elevated temperature and red, swollen, painful joints. During another pregnancy, two years later, she died, undelivered, of heart failure associated with an attack of rheumatic fever.

The patient was born with red, painful, swollen joints which caused him to cry out when gentle passive motion was attempted. These observations were attested by the father and the attending physician, Dr. E. C. Beam, of Columbus, Ohio, who also heard abnormal heart sounds and recognized the presence of a cardiac pathologic process on his first examination, which was made thirty minutes after the infant's birth. The diagnosis of rheumatic fever with rheumatic heart disease was made, and the patient remained under the care of this physician until 1929, when he was referred to our clinic. The child had had dyspnea since birth, and there was evidence of heart failure during a mild tonsillitis and measles in 1928. At the age of 6 months the symptoms in the joints disappeared, and from that time there were no manifestations of active rheumatic fever.

Examination.—The patient was a fairly well developed white boy, who weighed 58 pounds (26,300 Gm.) and was 9 years of age. There was slight cyanosis of the lips and fingers, and moderate dyspnea and orthopnea were present. The veins in the neck were congested, and marked swinging pulsations were seen over the carotid arteries. A marked pulsation was noted over the xiphoid process, but the apex beat was diffuse and in the fifth and sixth interspaces 8 cm. to the left of the midsternal line. There was a marked thrill at the apex, which was also felt in the fourth interspace to the right of the sternum. The cardiac dulness was as follows: The left border was 10 cm. to the left of the midsternal line in the fifth and sixth interspaces, and 6 cm. to the left of this line in the third interspace, while the right border was 5 cm to the right of the midsternal line in the fourth interspace.

A loud, rough diastolic murmur was heard at both the aortic and the pulmonic areas, and at the mitral area there was a soft blowing murmur heard through a flat first sound; there was also a rough diastolic murmur present. At the tricuspid area there was a soft blowing systolic murmur and a rough diastolic murmur. The heart rate was 112, and the rhythm was regular. There were moist râles heard in the bases of both lungs, and the liver was tender and extended 3 cm. below the costal margin. The abdomen was distended owing to moderate ascites. Both the fingers and the toes revealed marked clubbing, and the edema of the feet and ankles was moderate.

The cardiac measurements by means of the orthodiagram were: longitudinal, 15.6 cm.; horizontal, 15. cm.; base, 13.4 cm.; left ventricle, 9.5 cm.; bisector, 1.7 cm.; right ventricle, 15.6 cm.; right auricle, 8.7 cm., and left auricle, 5.2 cm. The

electrocardiogram (fig. 1) was interpreted as showing sinus tachycardia, myocardial insufficency and right axis deviation. The laboratory findings were: urine, specific gravity, 1.008; urinary albumin, 50 mg.; urinary sugar, negative; Wassermann reaction, negative; blood sugar, 75 mg.; blood count, hemoglobin, 90 per cent, red blood cells, 4,500,000 and white blood cells, 8,600 per cubic millimeter.

Course.—The child remained in the hospital for a month and improved with rest and digitalis therapy, so that he could be discharged. During this time his only complaints were dyspnea and limited capacity for effort. His temperature did not exceed 98.4 F., and his respirations were from 20 to 32.

The clinical diagnosis was: rheumatic heart disease, hypertrophy and dilatation, myocardial insufficiency, panvalvulitis, mitral stenosis and insufficiency, tricuspid stenosis and heart failure with fourth degree function.

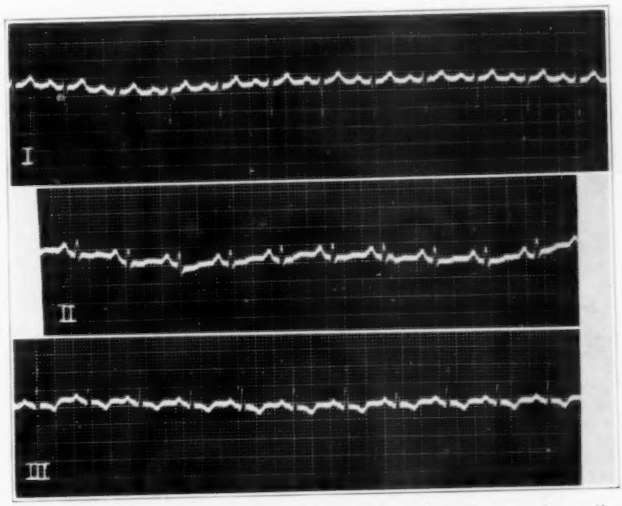

Fig. 1.—Electrocardiogram interpreted as disclosing sinus tachycardia, myocardial insufficiency and right axis deviation.

Six months later the child was again admitted to the hospital because of heart failure and with essentially the same findings, except that the cyanosis, dyspnea and orthopnea were more severe. At this time the edema extended to the knees, and the ascites was increased. The child did not respond to rest and digitalis therapy, and abdominal paracentesis had to be repeatedly performed. On Dec. 18, 1929, he died suddenly following this procedure.

Autopsy (Dr. R. S. Fidler).—Autopsy was performed thirty minutes after death. The body, which was not embalmed, was that of a well developed white boy about 10 years of age. There was marked edema of the entire body; especially noticeable were a large barrel-shaped abdomen and marked bilateral edema of the legs. There was edema of the prepuce, which formed a mass the size of a large walnut. The trocar puncture wound of a recent paracentesis was found approximately in the midline of the abdomen just above the pubis.

On incision through the skin and tissues of the thorax and abdominal wall, a marked subcutaneous edema was found. About 5 liters of a clear, straw-colored fluid, which coagulated on standing, filled the abdominal cavity, and each pleural cavity contained about 600 cc. of a similar fluid. The liver was enlarged and extended 2 cm. below the costal margin. The kidneys were normal in size; the capsule stripped easily, revealing a smooth, normal cortex, and on cut section the

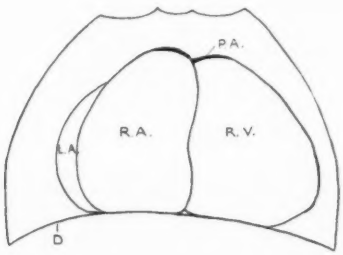

Fig. 2.—Diagram of the front view of the heart in the thorax: *P. A.*, pulmonary artery; *R.V.*, right ventricle; *R.A.*, right auricle; L.A., left auricle; *D.*, diaphragm.

Fig. 3.—View of the heart showing the small opening in the pulmonary valve.

markings were well defined. The remaining viscera of the abdomen presented no noteworthy pathologic process.

On removal of the sternum, the heart was found to extend well beyond the right of the sternum, and it measured 17 cm. in the widest transverse diameter. The pericardial sac contained about 300 cc. of a clear straw-colored fluid. The parietal pericardium was smooth and glistening, except over the region of the right auricle, where it was marked with many petechial hemorrhages. Similar

hemorrhages were found on the visceral pericardium over the left ventricle. The heart had rotated to such a degree and position that the left auricle was posterior and extended to the right so as to form the right border of the heart (fig. 2). The large right auricle was in front and with the right ventricle formed the anterior surface of the heart. These two chambers gave the heart its greatly increased transverse diameter. The left ventricle was small and entirely posterior. Owing to the accumulation of fluid within the pleural cavities and the enormous size of the heart, the lungs were partly collapsed but were crepitant throughout. Permission for autopsy did not include an examination of the brain.

When the heart was empty of blood, it weighed 320 Gm. and measured 9.5 cm. across the base. The right auricle was markedly dilated, measuring 9 by 8 by 8 cm., with accompanying wide separation of the muscle bundles. The tricuspid valve was open, admitting the index finger, and the leaflets were thickened and hard, while their chordae tendineae were shortened and the papillary muscles thickened. The cavity of the right ventricle measured 4.5 by 4 cm., and the myocardium varied from 7 to 14 mm. in thickness and was firm. The pulmonary valve was closed, and its cusps were thickened and fibrous, but when forced open from below a maximum opening of 4 mm. was produced, while in width the valve measured 3.5 cm. (fig. 3). The left auricle was small; it measured 3 by 3.5 by 3.5 cm., and the wall was of uniform thickness. The mitral valve was stenosed by a thickening on the auricular surface which gave it the typical button-hole appearance. The chordae tendineae were shortened and the papillary muscles thickened. The left ventricle was relatively small with a cavity measuring 3.5 by 2 cm., and the wall was 9 mm. in thickness with a firm myocardium. The cusps of the aortic valve were moderately thickened, so that when the valve was closed an opening 2 mm. in diameter remained. The entire valvular area measured 2.5 cm. in width. The aorta was smooth with both coronary orifices open, and dissection of these arteries revealed no noteworthy pathologic process.

Microscopic examination of the tissues from the heart revealed the following: The mitral valve showed many Aschoff bodies scattered throughout the fairly well vascularized scar tissue which had replaced the normal tissue and produced tremendous thickening of the leaflets. The aortic valve revealed definite fibrosis with few nuclei and no Aschoff bodies. The pulmonary valve showed thickening by the production of a loose granular tissue covering its auricular surface, and scattered throughout were mononuclear cells, but none were grouped in such a way as to suggest the formation of Aschoff bodies. The leaflets of the tricuspid valve were compact, less vascular and thickened. The ventricles showed some increase in the intermuscular fibrous tissue, which was loose in character. The right auricle revealed an Aschoff body and considerable interfibrillar scar tissue.

COMMENT

The case reported by Guthrie [5] is frequently cited in the consideration of intra-uterine rheumatic fever, but it cannot enlighten the subject, as the mother did not have rheumatic fever until three days after delivery, and the child contracted the disease when 11 days old. In the other three cases mentioned, all the mothers had rheumatic fever at the time of delivery; in the case reported by Ferguson, the child had the disease at birth; in the case reported by Pocock, the condition was recognized within thirty hours, and in that reported by Schaefer, it developed three

days after birth. There was no cardiac damage found in any of these cases; the case reported by Ferguson was the only one in which an autopsy was performed. An analysis of these cases reveals evidence that supports the probability of intra-uterine transmission of rheumatic fever but does not prove that it can occur.

The case herein reported describes a child who was born with active rheumatic fever and a cardiac lesion, and whose mother had suffered from this disease throughout her pregnancy. These facts were affirmed by the husband and the attending physician, and at the autopsy nine years later the heart disease was demonstrated to be rheumatic with no evidence of congenital anomalies. Therefore it is obvious that the intra-uterine transmission of rheumatic fever and heart disease is not only probable, but possible.

SUMMARY

A case of intra-uterine rheumatic fever is reported.

It is evident from the analysis of this case that rheumatic heart disease can occur before birth.

Autopsy revealed the right side of the heart to be greatly dilated and it had rotated in such a manner that the left auricle formed the right border of the heart.

ADIPOSITY OF THE HEART

A CLINICAL AND PATHOLOGIC STUDY OF ONE HUNDRED AND THIRTY-SIX OBESE PATIENTS

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The diagnosis of fatty heart was frequently made by clinicians in the past generation, but in recent years investigators have, to a large extent, avoided the problem. Considerable confusion has arisen from the use of such terms as fatty degeneration, fatty infiltration, fatty metamorphosis, adiposity of the heart (cor adiposum or adipositas cordis) and obesity of the heart.

In the past, two distinct conditions have commonly been confused, and both have been alluded to as fatty heart. These are (1) the state in which there is an abnormal increase in the amount of fat in the subepicardial connective tissue and in which penetration or infiltration of fat into the connective tissue lying between the muscle bundles and the muscle fibers takes place and (2) the state in which fatty changes take place within the cell (cytoplasm) and which most pathologists [1] believe to be the result of a diminished utilization (oxidation) of the fat normally brought to the muscle cell.

According to Pratt,[2] Harvey in the seventeenth century published the first observation on fatty heart; on dissecting the body of a very corpulent man he found the heart completely covered with fat (cor adipe plane tectum). In recording the findings at necropsy of the body of Parr, Harvey [3] described the heart as being large, thick and fibrous, and containing a considerable quantity of adhering fat, both in the circumference and over the septum, but he did not attribute the patient's death to this cause.

From the Section on Cardiology, the Mayo Clinic.

1. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914, p. 677.

2. Pratt, J. H.: On the Causes of Cardiac Insufficiency, Bull. Johns Hopkins Hosp. **15**:301 (Oct.) 1904.

3. Harvey, William: Anatomical Examination of the Body of Thomas Parr, in Harvey, William: Works of William Harvey, translated from the latin by Robert Willis, London, Sydenham Society, 1847, p. 589.

Both varieties of fatty heart, wrote Pratt, were recognized by Corvisart [4] and were described by Laennec,[5] but the first careful anatomic studies of the conditions were made by Quain [6] and Rokitansky.[7] One of the first recorded cases in which there was present a condition that was assumed to be fatty degeneration was the case studied and reported by John Cheyne,[8] in 1818. This case is of historic interest not only because it is a carefully recorded instance of fatty metamorphosis but also because it was the first case in which the peculiar type of respiration, now known as Cheyne-Stokes respiration, was described. At that time, Cheyne-Stokes breathing was thought to be almost pathognomonic of fatty heart. We believe that the clinical picture that Cheyne described was not actually that of fatty heart but that of arteriosclerosis, coronary sclerosis and probably previous hypertension.

Many observers now agree with the views advanced by Rosenfeld [9] and Herxheimer [10] that the fatty change that occurs within the cytoplasm of the cell, so-called fatty degeneration, is in reality an infiltrative process rather than true degeneration and is probably the result of two causes: a disturbance of cellular nutrition and toxemia. Owing to the general acceptance of this view, the term fatty infiltration is commonly used to describe the two dissimilar conditions. Because of the generally accepted view that the fatty changes which occur within the cell are infiltrative, we believe, as pointed out by Beattie and Dickson,[11] that an increase in the amount of fat in the subepicardial connective tissue and in the connective tissue lying between the muscle bundles and muscle fibers is best designated as adiposity of the heart. This term will be used throughout the remainder of this article.

Most of the literature of recent years deals chiefly with the fatty changes occurring within the cytoplasm of the cells, and little investi-

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4. Corvisart, J. N.: An Essay on the Organic Diseases and Lesions of the Heart and Great Vessels, Philadelphia, A. Finley, 1812, p. 153.

5. Laennec, R. T. H.: A Treatise on Diseases of the Chest, New York, S. S. and W. Wood, 1838, p. 682.

6. Quain, R.: Fatty Diseases of the Heart, Med. Chir. **33**:120, 1850.

7. Rokitansky, Carl: A Manual of Pathological Anatomy, London, Sydenham Society, 1852, vol. 4, p. 204.

8. Cheyne, John: A Case of Apoplexy in Which the Fleshy Part of the Heart was Converted into Fat, Dublin Hosp. Rep. **2**:216, 1818.

9. Rosenfeld, Georg: Über die Herzverfettung des Menschen, Zentralbl. f. inn. Med. **22**:145 (Feb. 9) 1901.

10. Herxheimer, Gotthold: Über Fettfarbstoffe, Deutsche med. Wchnschr. **27**:607, 1901.

11. Beattie, J. M., and Dickson, W. E. C.: A Text-Book of Special Pathology, London, Rebman, 1909, p. 522.

gative work has been done concerning the subject of adiposity of the heart. This is particularly true regarding the histologic pathology of these conditions. In a recent textbook [12] on pathology, the subject of adiposity of the heart is dismissed with one sentence, "Adipose tissue extends through the wall of the heart and appears under the endocardium," and several pages are devoted to the fatty changes that occur within the cell. In a recent book on diseases of the heart,[13] less than one page is devoted to the subject of fatty heart.

MATERIAL

One hundred and thirty-six patients on whom postmortem examinations were conducted formed the basis of this study. The only criterion utilized in our selection of material was the definite establishment of the fact that the patients were obese. In the cases selected, the increase in body weight was 13 per cent or more; the computations were made by the use of standard actuarial charts on the basis of age, sex, height and body weight.

The minimal degree of excess body weight in our cases was 13 per cent (9.1 Kg.); the maximal degree, 170 per cent (157.3 Kg.), and the average, 45 per cent (32.3 Kg.). Our minimal criterion of 13 per cent is conservative, for the accepted minimum is only 10 per cent (table 1).

Death was caused by a great variety of diseases, and we were thus able to study hearts that were presumably normal as well as those that were invaded by disease. The age of the patients ranged from 10 months to 75 years, the average age being 52.1 years. There were three children in the series—an infant aged 10 months and two boys aged, respectively, 10 and 14 years—who were excluded from the computations of the weight of the body and the heart. The distribution of the cases according to decades of life occurred in the following manner: first decade, one case; second decade, two cases; third decade, four cases; fourth decade, ten cases; fifth decade, twenty-seven cases; sixth decade, fifty-six cases; seventh decade, thirty-one cases, and eighth decade, five cases. There were ninety-four females and forty-two males, an approximate ratio of 7 : 3.

METHOD

This investigation necessitated the determination of certain basic data in all cases, in addition to the data already mentioned. It was necessary to obtain the weight and the height of the body and the weight of the heart. From these factors we derived the ratio of cardiac weight to body weight, and included the determination of the surface area of the body in our computations.

Quantitative determinations of fat of the heart muscle were made and compared with those for normal hearts of patients of normal body weight. Numerous sections of heart muscle which had been stained for fat were studied comparatively.

Special attention was given to certain clinical and associated pathologic findings that occurred with unusual regularity throughout the series. It was found advisable,

12. MacCallum, W. G.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1932, pp. 81, 88 and 448.

13. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931, p. 438.

for comparative purposes, to divide our cases into groups, and they will be so considered in the remainder of this study: group 1, fifty-two cases of obesity without demonstrable evidence of heart disease; group 2, nine cases of obesity without demonstrable evidence of heart disease but with varying degrees of cardiac insufficiency; group 3, sixty cases of obesity with hypertension, and group 4, fifteen cases of obesity with miscellaneous conditions, such as nine cases of coronary sclerosis, two cases of hepatic cirrhosis, one case each of aortic stenosis, syphilitic aortitis and previous exophthalmic goiter, and one case in which there was a dilated and hypertrophied heart of indeterminate origin.

TABLE 1.—*Percentage and Actual Increase in Body Weight Above the Normal in One Hundred and Thirty-Five Cases* *

	Excess Body Weight			Excess Body Weight			Excess Body Weight			Excess Body Weight		
Cases	Per Cent	Kg.	Cases	Per Cent	Kg.	Cases	Per Cent	Kg.	Cases	Per Cent	Kg.
1	13	13.6	35	..	23.2	69	42	26.8	103	58	39.5
2	..	9.1	36	..	21.8	70	..	29.5	104	59	37.3
3	14	9.5	37	..	21.4	71	..	31.4	105	60	24.5
4	..	9.5	38	32	22.7	72	43	28.6	106	..	43.2
5	15	14.1	39	..	21.8	73	44	31.4	107	..	36.8
6	..	13.2	40	..	23.6	74	..	38.6	108	62	40.0
7	16	13.2	41	33	46.4	75	..	28.2	109	64	39.1
8	17	14.5	42	..	25.0	76	45	31.4	110	66	45.9
9	..	15.9	43	..	20.5	77	..	29.5	111	67	43.6
10	18	11.8	44	34	25.5	78	..	28.2	112	..	43.2
11	19	13.2	45	35	24.1	79	..	31.4	113	68	40.0
12	21	13.6	46	..	25.0	80	..	28.2	114	69	46.4
13	22	14.1	47	..	25.0	81	..	34.1	115	..	44.5
14	..	17.7	48	..	24.5	82	47	36.4	116	..	44.5
15	23	13.6	49	..	24.5	83	..	29.1	117	70	44.5
16	24	19.5	50	36	28.2	84	48	36.8	118	72	55.0
17	..	20.9	51	..	24.1	85	48	29.5	119	74	53.2
18	25	17.7	52	..	22.3	86	51	31.8	120	75	54.5
19	..	16.4	53	37	27.7	87	52	29.5	121	77	66.8
20	..	18.2	54	..	31.8	88	..	35.0	122	78	55.9
21	..	19.1	55	..	46.4	89	53	44.1	123	79	50.0
22	..	20.0	56	..	46.4	90	..	36.4	124	..	53.2
23	..	17.7	57	38	25.5	91	..	39.5	125	81	70.9
24	26	18.6	58	..	32.7	92	..	34.5	126	83	44.5
25	..	19.1	59	..	28.6	93	..	36.4	127	..	56.8
26	27	20.0	60	..	29.5	94	54	41.8	128	84	62.3
27	..	16.8	61	..	30.0	95	..	36.8	129	87	62.3
28	28	23.6	62	39	25.5	96	..	37.7	130	89	32.7
29	28	17.7	63	..	30.0	97	55	34.5	131	96	66.8
30	29	22.7	64	..	25.5	98	..	48.2	132	100	68.2
31	..	20.9	65	..	34.5	99	56	33.6	133	101	75.0
32	30	19.5	66	40	28.2	100	..	34.1	134	103	69.0
33	..	19.5	67	41	29.1	101	57	36.4	135	170	157.3
34	31	23.6	68	..	28.2	102	..	36.4			

* An infant, aged 10 months, was excluded.

NORMAL CARDIAC WEIGHTS

In order properly to interpret the weight of the heart in obesity it is necessary to know the weights of normal hearts of persons of normal stature and body weight. In 1928, one of us (Smith [14]) recorded such observations in one thousand cases. It was found that the average weight of the heart of the adult male was 294 Gm., whereas that of the adult female was 250 Gm.

14. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body, and of the Weight of the Heart to Age, Am. Heart J. **4**:79 (Oct.) 1928.

A definite correlation between the weight of the heart and the weight of the body was determined; the ratio for males was found to be 0.43 per cent and that for females, 0.4 per cent. It was also found to be possible to calculate the weight of the heart from the weight of the body with an error varying from 8 to 10 per cent. In males the body weight in pounds is multiplied by the ratio 1.96 for the average, 1.5 for the minimum and 2.3 for the maximum; these ratios are applicable only for average body weights and are lower if persons are of increased body weight. For obese patients the ratios to be used are 1.5 for females and 1.6 for males.

The weight of the heart was found to increase with increases in the weight of the body. If the body weight remained stationary as the age increased, the weight of the heart did not increase with the added years. This, of course, does not apply to children.

STUDIES OF CARDIAC WEIGHT

Obesity Without Other Demonstrable Evidence of Heart Disease.—In fifty-two cases of our series, careful study of the hearts failed to reveal evidence of heart disease other than the abnormal deposition of fat, which will be considered separately in this paper. In none of the cases was there hypertension or positive evidence that hypertension had previously existed. In no instances were there any significant changes in the coronary arteries. These cases, therefore, so far as this investigation is concerned, furnish basic data relative to the weight of the heart in obesity.

The minimal degee of excess body weight was 13 per cent (13.6 Kg.), and the maximal, 103 per cent (69 Kg.), while the average increase was 43 per cent (29.5 Kg.). The average age of the patients was 49.3 years; the youngest was 10 months of age, and the oldest, 72 years. The cases were distributed in the various age periods as follows: first decade, one case; second decade, two cases; third decade, two cases; fourth decade, four cases; fifth and sixth decades, each sixteen cases; seventh decade, nine cases, and eighth decade, two cases. There were thirty-five female patients and seventeen male patients, a ratio of 2:1.

The average ratio of cardiac weight to body weight for the group was 0.38 per cent, whereas that for male patients was 0.41 per cent, and that for female patients, 0.35 per cent. These ratios are definitely less than those obtained when persons are of normal body weight (males, 0.43 per cent; females, 0.4 per cent).

Owing to the fact that this group of patients is small, we deem it advisable to utilize the average ratio of cardiac weight to body weight, instead of using the ratios differentially, as they occur according to sex.

The ratio of cardiac weight to body weight was less than 0.38 per cent in thirty cases (58 per cent), exactly 0.38 per cent in three cases

(6 per cent) and more than the average in nineteen cases (36 per cent). The range extended from 0.22 to 0.55 per cent (table 2).

The actual cardiac weights in this group revealed interesting data. The average cardiac weight was 376 Gm., a great increase over the

TABLE 2.—*Data Pertaining to Cardiac Weight and Body Weight in Fifty-Two Cases of Obesity Without Demonstrable Evidence of Heart Disease*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calculated	Variation	
10 mos.	F	0.22	64	11.4	25	38	−13	
59	F	0.29	163	136.4	395	450	−55	2.31
59	F	0.29	157	92.3	268	305	−37	1.92
38	F	0.30	178	113.6	345	375	−30	2.30
45	F	0.30	154	98.2	292	324	−32	1.94
63	F	0.30	163	88.6	262	293	−31	1.93
35	F	0.31	169	113.6	357	375	−18	2.20
46	F	0.32	143	86.4	280	285	− 5	1.74
49	F	0.32	163	93.2	295	308	−13	1.97
42	M	0.32	175	131.8	415	464	−49	1.75
50	F	0.33	165	100.5	329	332	− 3	2.06
37	F	0.34	161	90.9	307	300	+ 7	1.93
60	F	0.34	165	96.9	326	320	+ 6	2.02
50	F	0.34	167	100.0	310	330	−20	2.09
40	F	0.34	163	84.1	284	278	+ 6	1.88
57	F	0.35	159	95.5	350	315	+35	1.96
44	F	0.35	169	95.0	331	314	+17	2.04
57	F	0.35	171	94.5	331	312	+19	2.06
72	F	0.35	156	109.1	388	360	+28	2.04
43	F	0.36	163	82.7	296	273	+23	1.87
45	M	0.36	183	118.2	425	416	+ 9	2.37
53	F	0.36	161	100.0	330	300	+30	2.01
57	F	0.36	162	81.8	290	270	+20	1.86
62	F	0.36	167	127.3	450	420	+30	2.30
50	F	0.37	154	94.5	355	333	+22	1.91
10	M	0.37	153	57.7	215	203	+12	1.53
60	M	0.37	174	105.5	391	371	+20	2.18
51	M	0.37	179	101.8	380	358	+22	2.20
68	F	0.37	167	98.2	364	324	+40	2.06
60	F	0.37	166	93.2	349	308	+41	2.00
55	F	0.38	156	100.0	352	330	+22	1.97
49	F	0.38	167	95.5	365	315	+50	2.09
28	F	0.38	161	99.1	372	327	+45	2.00
29	M	0.39	173	94.1	367	331	+36	2.06
49	F	0.39	158	77.7	300	257	+43	1.79
65	F	0.39	168	90.9	357	300	+57	1.99
69	M	0.39	173	95.5	370	336	+34	2.09
43	M	0.41	171	115.5	470	406	+64	2.20
44	F	0.41	154	100.5	410	332	+78	1.96
43	M	0.41	172	102.3	420	360	+60	2.14
71	M	0.41	162	91.8	380	323	+57	1.95
50	M	0.41	183	118.2	484	416	+68	2.39
14	M	0.41	148	65.5	226	230	− 4	1.58
52	F	0.43	169	86.4	370	285	+85	1.96
27	M	0.43	180	113.6	488	400	+88	2.31
36	F	0.44	163	108.6	482	359	+123	2.11
60	F	0.44	162	89.1	390	294	+ 96	1.93
51	M	0.45	172	98.2	450	346	+104	2.10
56	M	0.49	173	101.4	493	357	+136	2.14
48	M	0.52	188	106.8	551	376	+175	2.32
41	M	0.53	184	109.1	572	384	+188	2.30
56	F	0.55	152	81.8	445	270	+175	1.77

normal cardiac weights of persons of normal body weight. The average weight of the hearts of the male patients was 444 Gm., an increase of 150 Gm. over that of the normal. The average weight of the hearts of the female patients was 345 Gm., an increase of 95 Gm. over the normal. The computations exclude the three children in the group.

In calculating the cardiac weight in this series according to the formula of Smith, it was found that the actual cardiac weight was less

than the calculated cardiac weight in thirteen cases (25 per cent), and that the average ratio of cardiac weight to body weight in these cases was only 0.31 per cent. The actual cardiac weights in this group of eleven cases (two children being excluded) ranged from 268 to 415 Gm., and the average cardiac weight was 322 Gm. The latter value is 64 Gm. less than the average for the group. The data clearly demonstrate that the weights of the hearts of an appreciable proportion of obese persons is less than that demanded by the height and weight of the body. This fact in itself may be responsible to a considerable degree for the fairly common apparent circulatory inadequacy of obese persons.

In the majority of cases (75 per cent), however, the actual cardiac weights considerably exceeded the calculated cardiac weights; the average weight was 383 Gm., an average excess over the calculated average of 56 Gm. The range of actual cardiac weights was from 284 to 572 Gm. The findings indicate that the majority of obese persons, when heart disease other than abnormal deposition of fat is absent, have hearts that exceed in weight those of persons of normal body weight. The cardiac weight tends to parallel the increase in body weight to a certain point (about 104.5 Kg.), and when the body weight increases beyond this, the cardiac weight does not increase proportionately.

A correlation between average cardiac weight and surface area of the body was evident. This of course was anticipated, in view of the correlations of cardiac weight and body weight. Spreads of surface area of from 1.74 to 1.99 square meters were accompanied by an average cardiac weight of 335 Gm. In cases in which the surface area ranged from 2 to 2.19 square meters, the average cardiac weight was 376 Gm. In the surface area spreads of from 2.2 to 2.39 square meters, the average cardiac weight was 447 Gm.

The fifty-two cases just considered will be referred to hereafter as the control group.

Obesity Without Demonstrable Evidence of Heart Disease but With Varying Degrees of Cardiac Insufficiency.—These cases, although only nine in number, were of unusual interest to us, owing to the fact that the usual forms of heart disease were absent, yet the patients presented signs and symptoms of cardiac insufficiency. Four patients had congestive heart failure.

Analysis of this group was critical, and we believe that diseases capable of producing cardiac hypertrophy, including hypertension, were excluded. So far as it is possible for us to ascertain, the patients represented instances of varying degrees of heart failure, the result of obesity.

The youngest patient was 33 years of age, and the oldest, 74; the average age was 51.5 years. There were two men and seven women.

The average degree of excess body weight in this group of cases was 60 per cent (20.5 Kg.), considerably more than that in the previous group (43 per cent). The minimal increase in body weight was 14 per cent (9.5 Kg.), and the maximal increase was 170 per cent (157.3 Kg.).

The average ratio of cardiac weight to body weight was 0.39 per cent, a slight increase over that in the control group, but lower than the normal average established by Smith. The average actual cardiac weight in these cases was 450 Gm., or 74 Gm. more than that in the control group. The calculated average cardiac weight was 399 Gm., or 51 Gm. less than the actual average cardiac weight (table 3),

Although this group of cases was small, a definite correlation between the weight of the heart and of the body occurred, but the rela-

TABLE 3.—*Data Pertaining to Cardiac Weight and Body Weight in Nine Cases of Obesity Without Demonstrable Evidence of Heart Disease but with Varying Degrees of Cardiac Insufficiency*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calculated	Variation	
49	F	0.30	151	94.1	284	311	— 27	1.88
44	F	0.36	158	90.9	324	300	+ 24	1.92
58	M*	0.36	184	122.7	435	432	+ 3	2.41
44	F	0.37	156	90.9	339	300	+ 39	1.89
59	F	0.37	166	80.0	302	264	+ 38	1.87
74	F*	0.39	172	101.8	394	336	+ 58	2.12
33	M*	0.41	194	250.0	929	880	+ 49	3.00+
50	F*	0.42	168	127.7	532	422	+110	2.32
53	F	0.49	163	104.5	510	345	+165	2.09

* Patients with congestive heart failure.

tively lowered cardiac weights with extreme instances of obesity, as shown in the control group, did not occur; in only one case was the actual cardiac weight less than the calculated weight. This, we believe, indicates that cardiac enlargement beyond certain limits in obesity, as well as in other conditions, results in circulatory inadequacy leading to cardiac failure. It is of interest in this connection to comment on the case of the man, aged 32 years, who weighed 250 Kg. and whose height was 194 cm. The cardiac weight of this patient was 929 Gm., whereas the calculated weight of the body was 880 Gm. (table 3). He suffered from congestive heart failure which resulted in death. This is of course an extreme example, yet it agrees in all respects with our data concerning the total series.

The following correlations between the surface area of the body and the cardiac weight occurred: from 1.8 to 1.99 square meters, 312 Gm.; from 2 to 2.19 square meters, 452 Gm.; from 2.2 to 2.39 square meters, 532 Gm., and from 2.4 to 3 square meters, 682 Gm.

Obesity with Hypertension.—Sixty obese patients had well marked hypertension, giving us the opportunity to study hearts that theoretically should reveal hypertrophy and to compare these data with those obtained in the control group. The average readings of blood pressure in millimeters of mercury were 175 systolic and 82 diastolic.

The youngest patient was 32 years of age, and the oldest, 74; the average age was 54.1 years. The cases occurred in the various age periods in the following manner: fourth decade, four cases; fifth decade, seven cases; sixth decade, thirty-one cases; seventh decade, seventeen cases, and eighth decade, one case. There were forty-five women and fifteen men, a ratio of 3:1.

The average degree of excessive body weight of the patients was 44 per cent (31.4 Kg.), the minimal was 13 per cent (9.1 Kg.) and the maximal was 101 per cent (75 Kg.).

The average ratio of cardiac weight to body weight was 0.45 per cent, a considerable increase over that in the control series (0.38 per cent). The ratios ranged from 0.29 to 0.77 per cent (table 4). The highest value in the control group was 0.55 per cent. The ratio of cardiac weight to body weight was below 0.38 per cent (our established normal for obese patients) in fourteen cases (23 per cent), exactly 0.38 per cent in three cases (5 per cent) and more than this value in forty-three cases (72 per cent). The average actual cardiac weight in this group was 467 Gm., an increase of 91 Gm. over the average in the control group. The lowest actual cardiac weight was 283 Gm. and the greatest weight, 807 Gm. (table 4).

These figures clearly illustrate the effect of hypertension on the heart in obesity, the cardiac weights unmistakably indicating cardiac hypertrophy of considerable degree. This fact is further emphasized when the individual cardiac weight, as well as the average cardiac weight of this group, is compared with that in the control group (tables 2 and 4).

When the actual cardiac weights in the cases of hypertension are compared with the calculated cardiac weights, the degree of hypertrophy existing becomes apparent. The average actual cardiac weight was 467 Gm., whereas the average calculated cardiac weight was 344 Gm., a difference of 123 Gm., as compared to a variation of only 39 Gm. in the control group. It is interesting to note the variations in the individual cases, as shown in table 4. A noteworthy fact is that the actual cardiac weight was less than the calculated cardiac weight in only eight cases (17 per cent), whereas in the control series the percentage was 25.

As would be anticipated, no definite correlation was evident between the weight of the heart and the increasing weight of the body in the obese patients with hypertension. In view of the fact that additional cardiac hypertrophy enters into the consideration of the cases and that the degree of cardiac hypertrophy obviously varies among individual

TABLE 4.—*Data Pertaining to the Cardiac Weight and Body Weight in Sixty Cases of Obesity with Hypertension*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calculated	Variation	
65	F	0.29	162	102.3	293	338	— 45	2.02
35	F	0.30	167	95.0	283	314	— 31	2.02
58	F	0.30	165	100.9	300	333	— 33	2.06
50	F	0.30	163	136.4	408	450	— 42	2.31
58	F	0.31	156	90.9	283	300	— 17	1.89
54	F	0.32	165	97.7	312	323	— 11	2.03
52	F	0.33	167	93.2	305	308	— 3	2.00
64	M	0.34	182	153.6	520	541	— 21	2.58
51	F	0.35	169	91.8	320	303	+ 17	2.01
61	F	0.35	160	90.9	320	300	+ 20	1.93
56	F	0.35	159	107.7	375	356	+ 19	2.06
56	F	0.36	177	114.5	416	378	+ 38	2.30
59	F	0.36	159	84.1	300	278	+ 22	1.86
44	F	0.37	169	136.4	500	450	+ 50	2.52
63	F	0.38	170	136.4	517	450	+ 67	2.39
33	F	0.38	160	94.5	360	312	+ 48	1.96
57	F	0.38	156	97.3	365	321	+ 44	1.95
49	F	0.39	159	100.5	390	332	+ 58	2.00
42	F	0.40	186	119.5	481	421	+ 60	2.41
59	F	0.40	175	90.9	366	300	+ 66	2.03
56	F	0.41	169	81.8	333	270	+ 63	1.92
56	F	0.42	165	90.9	383	300	+ 83	1.97
58	F	0.43	167	103.2	445	341	+104	2.10
53	F	0.43	162	105.0	450	347	+103	2.08
54	F	0.43	163	104.5	453	345	+108	2.02
66	F	0.43	157	104.1	450	344	+106	2.02
60	F	0.43	157	81.8	355	270	+ 85	1.82
38	F	0.44	171	95.5	421	315	+106	2.03
66	M	0.44	182	101.4	450	357	+ 93	2.21
32	M	0.44	189	127.3	590	448	+142	2.50
74	M	0.45	179	100.0	411	352	+ 59	2.19
59	F	0.45	180	100.5	448	332	+116	2.30
56	F	0.45	164	77.7	350	257	+ 93	1.83
59	M	0.45	177	105.9	475	373	+102	2.22
61	M	0.45	170	149.1	672	525	+147	2.49
50	F	0.45	171	97.3	435	321	+114	2.08
62	M	0.46	184	136.4	627	480	+147	2.53
60	M	0.47	184	109.1	510	384	+126	2.30
59	F	0.47	166	108.2	510	357	+153	2.12
67	M	0.48	175	108.2	520	381	+139	2.21
50	F	0.50	172	99.5	492	329	+163	2.11
63	F	0.50	146	72.7	365	240	+125	1.64
43	F	0.50	160	77.3	388	255	+133	1.80
48	F	0.51	158	113.6	575	375	+200	2.10
59	F	0.51	155	79.5	402	263	+139	1.78
66	M	0.51	172	100.9	513	355	+158	2.12
57	F	0.51	165	93.6	475	309	+166	1.99
61	F	0.53	178	109.1	579	360	+219	2.23
57	F	0.53	174	106.8	560	353	+207	2.20
56	F	0.56	166	98.6	552	326	+226	2.04
54	M	0.57	183	100.0	570	352	+218	2.21
52	F	0.57	166	99.5	567	329	+238	2.06
54	F	0.58	167	125.0	750	413	+337	2.29
65	M	0.59	172	109.1	638	384	+254	2.20
49	M	0.61	167	95.9	580	338	+242	2.03
68	M	0.62	188	109.1	679	384	+295	2.32
59	F	0.63	157	75.9	475	251	+224	1.75
63	F	0.65	164	125.0	807	413	+394	2.44
59	M	0.67	171	105.5	700	371	+329	2.16
42	F	0.77	158	84.1	643	278	+365	1.85

patients even of the same height and weight, parallelism could not be expected to occur. This observation enhances the validity of the correlations of cardiac weight to body weight in the control group.

The data occurred in the following manner: range of surface area from 1.6 to 1.89 square meters, 396 Gm.; from 1.9 to 2.09 square meters, 399 Gm.; from 2.1 to 2.29 square meters, 545 Gm.; from 2.3 to 2.49 square meters, 549 Gm., and from 2.5 to 2.59 square meters, 559 Gm.

Obesity with Various Forms of Heart Disease.—This was a miscellaneous group of fifteen cases, comprising nine cases of coronary

TABLE 5.—*Fifteen Cases of Obesity with Various Forms of Heart Disease, and Hepatic Cirrhosis*

Age, Years	Sex	Ratio of Cardiac Weight to Body Weight	Height, Cm.	Body Weight, Kg.	Cardiac Weight, Gm.			Surface Area, Square Meters
					Actual	Calculated	Variation	
Coronary Sclerosis								
35	F	0.30	164	100.0	303	330	— 27	2.04
49	M	0.42	180	127.3	538	448	+ 90	2.41
68	F	0.43	159	109.1	470	360	+110	2.09
68	M	0.45	167	89.5	406	315	+ 91	1.97
23	F	0.46	152	98.2	447	324	+123	1.93
56	F	0.47	159	91.4	427	302	+125	1.93
57	M	0.49	167	134.1	657	472	+185	2.32
52	M	0.50	168	90.9	457	320	+137	2.00
75	F	0.51	160	109.1	550	360	+190	2.09
Aortic Stenosis								
66	M	0.78	176	102.3	800	406	+394	2.16
Syphilitic Aortitis								
66	M	0.58	184	159.1	922	560	+362	2.69
Previous Exophthalmic Goiter								
55	F	0.36	165	115.5	410	381	+ 29	2.18
Indeterminate								
29	M	0.51	167	120.5	615	424	+191	2.05
Hepatic Cirrhosis								
62	F	0.30	160	90.9	274	300	— 26	1.93
50	F	0.58	164	107.7	505	349	+112	2.11

sclerosis, one case of aortic stenosis, one case of syphilitic aortitis with aortic insufficiency, one case in which there previously had been exophthalmic goiter and one case of cardiopathy of indeterminate origin. There were also two cases of hepatic cirrhosis.

These cases will be briefly considered; the detailed data are presented in table 5. The average degree of excess body weight was 57 per cent (36.8 Kg.). The minimal excess was 25 per cent (17.7 Kg.) and the maximal excess was 87 per cent (62.3 Kg.).

The cases listed under coronary sclerosis were all marked examples of the disease; the degree of sclerosis was recorded as grades 3 and 4. There was no evidence of hypertension at the time of the last examination, and the average readings of blood pressure were 127 systolic and 71 diastolic. The youngest patient was 23 years of age, and the oldest,

75; the average age was 53.6 years. The patient who was 23 years of age was a woman suffering from juvenile myxedema of marked degree and who died of congestive heart failure. At the age of 4 years she had been severely ill with an unidentified infectious disease resulting in thyroiditis and evidently producing extensive arteritis of the coronary vessels. Nine patients (60 per cent) had coronary sclerosis. There were four men and five women. The average ratio of cardiac weight to body weight was 0.45 per cent, identical with that in the group with hypertension. The range was from 0.3 per cent to 0.51 per cent. The average actual cardiac weight was 473 Gm., which was 97 Gm. more than that in the control group. The minimal weight was 303 Gm. and the maximal weight, 657 Gm. The average calculated cardiac weight was 359 Gm., 114 Gm. less than the actual average cardiac weight. The remaining cases, isolated instances of disease, are detailed in table 5.

CERTAIN CLINICAL FEATURES

The average age of the entire group of obese patients at death was only 52.1 years, supporting actuarial data that the life expectancy in obesity is unfavorable. Only four patients attained the age of 70 or more. A marked predominance of female patients over male patients occurred, a ratio of approximately 2:1. These data also support the general belief that obesity is more common among women than among men.

The common association of cholelithiasis and obesity is well recognized, and in this series of cases the association occurred in fifty cases (37 per cent). Another disease frequently linked with obesity is diabetes mellitus, but only four cases (3 per cent) occurred in this series. Hypertension occurred in sixty cases (44 per cent). Heart disease, including the cases with hypertension, occurred in eighty-four cases (62 per cent).

As stated earlier in this paper, the patients who were investigated died from a great variety of causes, and only a few interesting facts in this connection will be considered. Death wholly attributable to heart failure occurred in only nineteen cases (14 per cent). The deaths occurred in cases in which there was associated primary cardiac disease, with the exception of three cases, which occurred in the group without demonstrable heart disease but with evidence of cardiac insufficiency.

That fatal pulmonary embolism occurred in twenty-six cases (19 per cent) is striking. This observation is in agreement with the general belief that obese patients as a rule constitute unfavorable surgical risks, and that the operative mortality in these cases is greater than the normal hazard. The tendency to circulatory inadequacy in cases of obesity, as already emphasized, may be partly contributory to the relatively high incidence of pulmonary embolism. Death resulting from pneumonia occurred in only nine cases (7 per cent).

COMMENT

Obesity is a term applied to a general condition in which there is an undue accumulation of fat in the normal regions for storage or the fat depots of the body. The more common regions for the storage of fat are the subcutaneous connective tissues, the omentum, the mesentery, the bone marrow, the extraperitoneal tissues, the tissues about the kidneys and the orbits and, to a less extent, the connective tissue beneath the epicardium. The subepicardial space is one of the regions in which fat in moderate amount is normally deposited. When excess deposits of fat occur in the subepicardial space and penetration or infiltration of fat into the connective tissues lying between the muscle bundles and sometimes between the individual muscle fibers is observed, the condition is designated by the term adiposity of the heart.

Distribution of Fat.—Fat is commonly deposited over the base of the heart, over the auriculoventricular groove, around the bases of the great vessels, along the distribution of the coronary arteries, along the intervetricular sulci and over the right ventricle, especially along its right border and anterior surface and at the apex. In practically all cases, more fat is deposited over the right ventricle than over the left. As a rule, the anterior surface contains more fat than does the posterior surface. An area on the posterior surface of the left ventricle, about half way between the apex and the base is, as a rule, the last area to be covered by fat. The subepicardial fat varies from slight increases above normal to extreme deposits which encase the entire heart with several layers of fat, in some portions measuring more than 2 cm. in thickness (fig. 1). In our series of cases there was an actual excess of epicardial fat in one hundred and twenty-nine cases (95 per cent). A slight increase of epicardial fat occurred in thirty-five cases (26 per cent), a notable increase of epicardial fat in seventy-seven cases (57 per cent) and an extreme increase of epicardial fat in seventeen cases (12 per cent). In six cases the amount of epicardial fat was not described in the postmortem protocols, and the hearts in these cases were not available for study. In one case the epicardial fat was normal in amount, but this heart also was not available for study.

Fat from the epicardium penetrated the muscle, and varying degrees of penetration occurred. As a rule, a correlation occurred between the excessive amount of epicardial fat and the amount of fat penetrating between the muscle bundles, but this was not uniformly true.

In all of the cases more fat was deposited in the wall of the right ventricle than in the wall of the left ventricle. In some of the extreme cases there were certain places where fat penetrated completely through the wall of the right ventricle, and fat was even deposited beneath the endocardium. In a few instances, the fat penetrated into the papillary

muscle of the right ventricle (fig. 2). As a rule, the fat penetrated the muscular walls in very irregular distribution. In some instances the line of demarcation between the cardiac muscle and the subepicardial fat was entirely obliterated. This was true only of the right ventricle. Involvement of the left ventricle was not so extensive in any instance. In a few cases, extreme deposits of fat were found on the right ventricle (fig. 3). It seems reasonable to believe that when fat is deposited in such quantities it is capable of interfering with the action of the heart.

Fig. 1.—A heart that is completely encased in layers of fat, varying from one to several centimeters in thickness: *a*, aorta; *b*, right coronary artery, and *c*, apex.

This extreme involvement, however, was not common. The right ventricular wall is much thinner than the left, and the same degree of penetration of fat into both walls would appear to be greater in the right. However, in almost every instance there was relatively and absolutely more fat in the right ventricle than in the left. In no instance did fat penetrate into the muscle of the left ventricle to the same degree that it penetrated into the muscle of the right ventricle, nor did we find it present in such quantities in the left ventricle as to lead us to believe

that it would in any way materially interfere with the function and activity of the left ventricle.

Observations were made on the deposit of epicardial fat and its relationship to the coronary arteries. In some instances the coronary arteries, especially the anterior descending branch of the left coronary

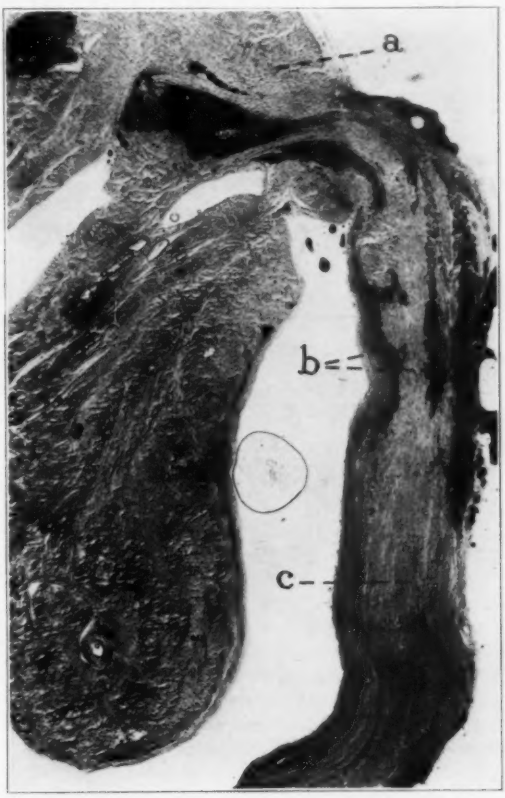

Fig. 2.—Cut section through the wall of the right ventricle and a papillary muscle; fat penetrating the papillary muscle may be seen. The wall of the right ventricle is indicated by *a*; the fat (black in photograph), by *b*, and the papillary muscle, by *c*. Frozen section; scarlet red stain (× 9).

artery, were found to lie entirely over fat; that is, the fat was situated between the artery and the cardiac muscle, and actually separated the artery from the muscle for a distance of about 2 cm. (fig. 3). In some instances the fat was deposited entirely over the artery, and in a few cases the fat was about equally deposited above and below the artery. The significance of these findings is uncertain.

In most instances a definite relationship between the excess of epicardial fat and the degree of general obesity occurred. The average excess body weight for the entire group was 32.3 Kg., and the average excess body weight in the cases in which there were extreme degrees of epicardial fat was 37.2 Kg.

Hearts which contain an excess amount of subepicardial fat are occasionally found at postmortem examination of persons who are not obese. We believe that the factors involved in the process are the same as those which occur in generalized obesity. The person has perhaps been obese at some previous time, or there may not be a sufficient deposit of fat generally to increase the body weight. No relationship was determined between the ages of the patients and the degree of epicardial fat. The hearts which contained the greatest deposits of fat were not those

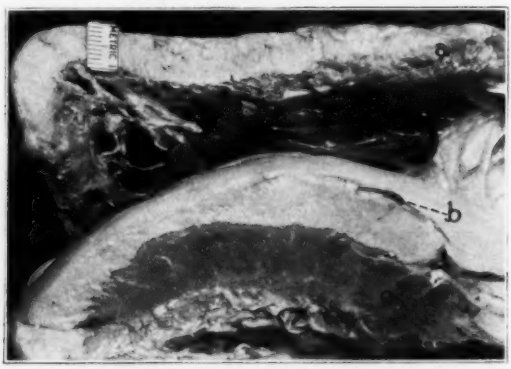

Fig. 3.—A cut section of the right ventricle where the subepicardial fat is 1 cm. in thickness is indicated by *a*. The line of demarcation between the fat and the muscle is almost completely obliterated. The anterior descending branch of the left coronary artery, separated from the muscle at a distance of 1 cm., is indicated by *b*, and a cut section of the wall of the left ventricle, by *c*. The line of demarcation between the fat and the muscle is distinct. The fat has not penetrated into the muscle as it has in the right ventricle.

of the oldest persons. The degree of excess of epicardial fat did not increase with the age of the patient; this finding is at variance with an often quoted statement that old persons often have very fatty hearts. No definite relationship occurred between the degree of subepicardial fat and the basic grouping of the cases as adopted in this study. The highest percentage (40 per cent) of extremely fatty hearts occurred in the group of nine cases in which there were varying degrees of heart failure. The group of sixty cases in which there was hypertension occurred next in order, and extreme fatty deposits were noted in 27 per cent. In the group of twenty-one cases in which there were various

types of heart disease, only 14 per cent showed extremely fatty hearts, and in the group of fifty-two cases in which cardiac disease was not demonstrable, only 17 per cent showed such hearts.

Normal cardiac muscle contains considerable fat. It has been estimated that the normal amount varies from 5 to 20 per cent of the total dry weight. According to Wells,[15] the fat is usually held in such form that it cannot be demonstrated by stains.

Master,[16] in 1923, found that normal hearts contain a certain amount of microscopically visible fat within the cytoplasm of the cells, and that the mere finding of small amounts of this fat does not warrant the pathologic diagnosis of fatty degeneration. He also found that the amount of this fat (within the muscle fiber) bears no relation to the age or to the state of nutrition of the patient at the time of death.

In our series, blocks of heart muscle were taken from various parts of the left ventricular wall and were analyzed for fat by Osterberg. The amount varied from 11.6 to 23.9 per cent. The average content of fat was 15.8 per cent. In a control series of persons of normal body weight, who had normal hearts, the content of fat varied from 12 to 20 per cent. Practically the same variation occurred as in the hearts of obese patients (table 6). In blocks of muscle taken from the right ventricle, in a region that contained an extreme amount of fat, as high as 40 per cent of fat was found.

In the total series examined microscopically for fat, no instance occurred in which the intracellular fat was increased.

There is considerable difference of opinion regarding the clinical significance of the forms of fatty heart (adiposity of the heart and fatty infiltration). Some authors believe that they are common and dangerous conditions. Others believe that these conditions do not exist.

We have pointed out that two distinct and separate conditions exist, and that they are usually included under the term fatty heart. The majority of pathologic studies have been confined to the fatty changes that occur within the cytoplasm of the cells. There is considerable question whether excessive fatty changes within the cells in any way interfere with cardiac function. Welch[17] observed rabbits which had been kept for some time at a high temperature, and which therefore were known to have fatty changes within the cells of the heart muscle; none had symptoms of cardiac derangement either at the time of the experiment or thereafter. He also found that the cardiac fibers that

15. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1920, p. 403.

16. Master, A. M.: Fatty Degeneration of the Heart, Arch. Int. Med. **31**:221 (Jan.) 1923.

17. Welch, W. H.: Cartwright Lectures on the General Pathology of Fever, M. News **52**:393, 1888.

contained an excess amount of fat within the cells contracted rhythmically. Hasenfeld and Fenyvessy [18] demonstrated that even when cardiac muscle was extremely fatty, following phosphous poisoning, the cardiac action was apparently unimpaired. This fact conforms with the condition presented in figure 4, which represents a case of extreme fatty degeneration (fatty changes within the cell). The patient died of carcinoma, and there was no evidence that cardiac insufficiency had been present at any time.

We believe that the excess of fat appearing within the cytoplasm of the cell, which is presumably due to diminished utilization of the fat brought to the cell and which is found in such conditions as phosphorus and chloroform poisoning, pernicious anemia, certain cachectic diseases and some infections, seldom interferes with cardiac function. We know

TABLE 6.—*Comparative Content of Fat of Heart Muscle of Twelve Obese Patients and Sixteen Patients of Normal Weight*

Obese Patients			Normal Patients:
Body Weight, Kg.	Overweight, per Cent	Content of Fat of Heart Muscle, per Cent	Content of Fat of Heart Muscle, per Cent
100.5	22	11.63	12.20
250.0	170	12.09	12.92
90.9	45	12.51	13.64
122.7	39	12.92	14.08
115.5	60	13.54	14.10
88.6	25	13.56	15.30
101.8	37	13.92	16.04
125.0	83	15.36	16.69
86.4	52	17.88	17.00
90.9	48	20.70	17.63
101.4	17	21.94	18.02
127.7	78	23.90	18.43
			18.50
			19.10
			19.80
			20.62

of no instance in which it has been proved that cardiac failure has resulted from this process alone, and we know of no way to recognize it clinically. This type of fatty heart, however, is not the subject of this study.

We believe that the part played by adiposity of the heart in producing cardiac failure is, in most instances, that of adding a burden to some other disease, such as hypertension or coronary sclerosis, and that any cardiac disease is distinctly more serious if cardiac adiposity is present. In some instances, although rarely, cardiac adiposity in itself is responsible for cardiac failure.

Christian [19] called attention to the great vascularity of adipose tissue. A thin-walled blood capillary is visible between almost every two fat

18. Hasenfeld, Arthur, and Fenyvessy, Béla: Ueber die Leistungsfähigkeit des fettig entarteten Herzens, Berl. klin. Wchnschr. **36**:80 (Jan. 23) 1899.

19. Christian, H. A.: Some Newer Aspects of the Pathology of Fat and Fatty Degeneration, Bull. Johns Hopkins Hosp. **16**:1 (Jan.) 1905.

cells. This intimate relationship between the blood capillary system and the fat cells must be important in the metabolic functions of fatty tissue. The adipose tissue is not to be regarded as merely a passive storehouse for fat, but rather as a diffuse, fatty, vascular organ in which great synthesis or catalysis of fat may take place.

We believe that there are many factors present, both local and general, that play a part in interfering with cardiac function in the presence of adiposity of the heart. A local process may be set up by the excess deposit of fat in the subepicardial space, by penetration of fat into the connective tissue lying between the muscle bundles, in some instances between the individual fibers, and by penetration of fat into the papillary

Fig. 4.—A section from the wall of the right ventricle; the fat droplets within the muscle fibers in longitudinal rows may be noted at *a*. The section is from the heart of a patient who had carcinoma of the stomach, but who had no symptoms or signs of cardiac insufficiency. Frozen section; scarlet red stain (× 550).

muscles. The penetration of fat may be so extreme as to interfere with the nutrition of the muscle or to impair the function of the muscle fibers. The actual separation of the muscle fibers by this excess amount of fat may interfere with myocardial function (figs. 5 and 6).

The effects of generalized obesity in producing cardiac impairment, we believe, are very important, and in the majority of instances this generalized effect is probably as important as the local effect, if not more so, in producing cardiac insufficiency. Generalized obesity promotes cardiac impairment by throwing an increased amount of work on the heart; there is an excessive amount of tissue to be nourished, there is

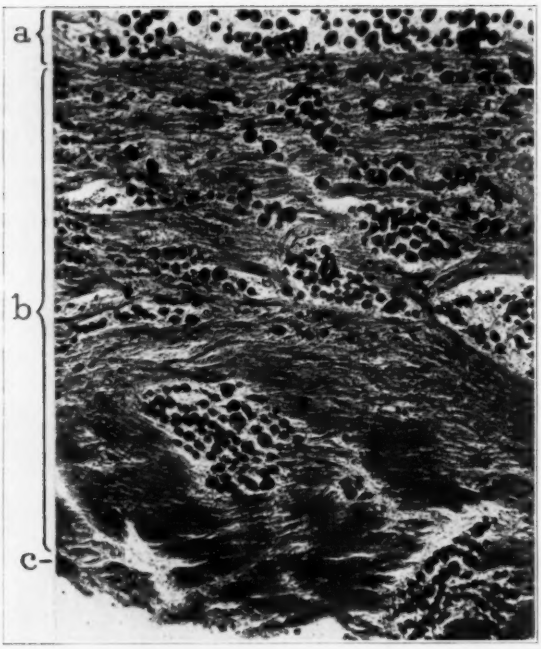

Fig. 5.—A cut section through the wall of the right ventricle. The fat shows black in the photograph. The epicardium is indicated by *a*; the wall of the right ventricle, by *b*, and the endocardium, by *c*. The fat has completely penetrated the wall. Frozen section; scarlet red stain (× 32).

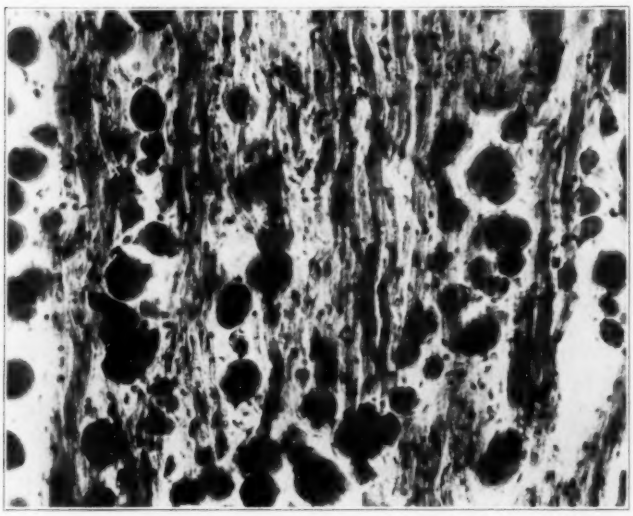

Fig. 6.—A section of the wall of the right ventricle, showing a higher magnification than that in figure 5. Frozen section; scarlet red stain (× 125).

an actual increase in the amount of work required in carrying around the excessive body weight, and the metabolic level of obese patients is increased.

SUMMARY

Doubtless many factors, both local and general, are concerned in the production of cardiac failure of obese patients. Local factors are the excessive deposit of fat in the subepicardial space and its penetration between the muscle bundles and the individual muscle fibers. There may be other factors; at all events, this excessive deposit of fat, we believe, impairs the function of the heart by its interference with cardiac activity and with nutrition of the myocardium. General factors are the increased amount of work to be performed by the heart, the excess amount of tissue to be nourished and the increased metabolism of the patients.

In obesity the weight of the heart increases and averages considerably more than that in subjects of normal weight. This increase in cardiac weight appears to be a physiologic necessity in order to permit circulatory adequacy when body weight and body surface increase. The weight of the heart keeps pace with the increasing weight of the body within certain limits, but fails to maintain this relationship in many cases in which body weight attains extreme proportions.

In a fourth of our cases of obesity in which demonstrable evidence of primary heart disease was lacking, the actual weight of the heart was less than the calculated weight, according to the formula of Smith. This observation suggests the fact that in certain cases of obesity the heart is not sufficiently large (although definitely larger than normal), and it is suggested that this status may be an appreciable factor in the apparent circulatory inadequacy so frequently evident in these cases.

When cardiac disease exists and the factor of additional cardiac hypertrophy is introduced, the correlation between cardiac weight and the increasing weight of the body is lost.

Nine cases of obesity were found in which evidence of primary cardiac disease was not demonstrable but in which symptoms and signs of varying degrees of cardiac failure occurred. Four patients had congestive heart failure, and three died of heart failure. These patients did not have hypertension, nor was there evidence that hypertension had existed previously. They were extremely obese; the average increase in body weight was 60 per cent, and the average cardiac weight was 450 Gm., only 17 Gm. less than the average in the group with hypertension.

These observations suggest the possibility that the large hearts in obesity, independent of associated pathologic changes, may occasionally fail and even result in death. However, obesity, both general and cardiac, more often is a contributory or additional factor in producing heart failure.

INSULIN RESISTANCE IN DIABETES MELLITUS

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From the earliest days of the use of insulin in the treatment of diabetes mellitus there have been reports of cases in which larger doses were required than the clinical condition of the patient seemed to warrant. Such cases were first described by Jaksch-Wartenhorst,[1] Mahler and Pasterny,[2] Umber and Rosenberg,[3] Falta,[4] Radoslav,[5] Pollak,[6] von Noorden and Isaac[7] and Matthes.[8] In the nine years since that time, numerous reports have revealed that in acidosis, in coma and in the presence of infection, hepatic disease or certain endocrine disorders the effectiveness of insulin may be decreased. Psychic disturbance and lack of exercise have been observed to raise the amount of insulin required. There are, however, many cases in which the poor response is unexplained.

"Insulin resistance" as the term describing relative ineffectiveness of insulin is commonly used, although there is as yet no general agreement as to its definition. Joslin[9] and Labbé[10] seem to confine its use

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1. Jaksch-Wartenhorst, R.: Insulin und Diabetes, Zentralbl. f. inn. Med. **45**:2 (Jan. 12) 1924.

2. Mahler, F., and Pasterny, K.: Klinische Beobachtungen über Insulin-Wirkung beim Diabetes mellitus, Med. Klin. **20**:337 (March 16) 1924.

3. Umber, F., and Rosenberg, M.: Zur Diagnose und Prognose der Glycosuria innocens, Ztschr. f. klin. Med. **100**:655, 1924.

4. Falta, W.: Ueber einen Insulinrefraktären Fall von Diabetes mellitus, Klin. Wchnschr. **3**:1315 (July 15) 1924.

5. Radoslav, C. M.: Ueber die Wirkung des Insulins auf den Blutzucker beim Menschen, Wien. Arch. f. inn. Med. **8**:395, 1924.

6. Pollak, L.: Ueber Insulinbehandlung, Wien. klin. Wchnschr. **37**:55 (Jan. 17) 1924.

7. von Noorden, C., and Isaac, S.: Weitere Erfahrung über Insulinbehandlung des Diabetes, Klin. Wchnschr. **3**:720 (April 22) 1924.

8. Matthes, M.: Ueber Insulin, Deutsche med. Wchnschr. **50**:487 (April 18) 1924.

9. Joslin, E. P.: Treatment of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1928, p. 633.

10. Labbé, M.: Existe-t-il des diabètes refractaires à l'insuline? Bull. Acad. de méd., Paris **97**:21 (Jan. 4) 1927; Les diabètes insulino-résistants, Rev. belge sc. méd. **3**:465, 1931.

to cases showing marked resistance to insulin, in which several hundred units a day are required for the elimination of glycosuria. Root,[11] in a recent review of the subject, calculated that a completely diabetic man should need about 200 units daily, and that a higher requirement should theoretically indicate resistance to insulin.

A broader definition of insulin resistance seems necessary, for many cases are seen in which such large doses are not required, yet the response of the blood sugar is disproportionately small. Radoslav [5] showed that cases of diabetes could be classed as normally insulin-sensitive, insulin-resistant or insulin-hypersensitive, according to the blood sugar curves following the administration of insulin during fasting. Discoverable complications are absent in many resistant cases. Rathery, Rudolf and T. and H. Villière [12] and Falta and Boller [13] recently reported a number of cases of resistance and commented on its frequency among their patients and the absence of demonstrable causes.

In a systematic study of over two hundred cases of diabetes in this hospital, it has been seen that relative resistance in the absence of complications is common and occurs in many patients not requiring extremely large doses of insulin. Knowledge of the degree of responsiveness to insulin has proved important in determining treatment. Five cases are reported to illustrate the method and value of distinguishing insulin-resistant from insulin-sensitive diabetes.

METHODS

Three methods were employed in studying these cases:

1. Determination of the ratio of the sugar excretion to the insulin requirement. The excretion of sugar per twenty-four hours is measured while the patient is receiving a standard diet of approximately 60 Gm. of protein, 160 Gm. of fat and 85 Gm. of carbohydrate. Insulin is then given in three approximately equal doses daily, and the amount required to eliminate glycosuria is determined. The relative effectiveness of the insulin may then be expressed by the ratio of the sugar excreted to the insulin required.

2. Omission test. Glycosuria is eliminated by insulin while the patient is receiving the standard diet, the regular daily requirement being determined. Then all insulin is omitted for twenty-four hours, and the resulting excretion of sugar is measured. The ratio of sugar excretion to insulin requirement gives a second method of estimating the dextrose equivalent.

3. Determination of the insulin tolerance. After the dosage necessary to keep the urine free from sugar is determined, the daily amount is gradually increased until hypoglycemic symptoms are provoked. The number of units of insulin above requirement which are tolerated without the appearance of hypoglycemia is called the insulin tolerance.

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11. Root, H. F.: Insulin Resistance and Bronze Diabetes, New England J. Med. **201**:201 (Aug. 1) 1929.

12. Rathery, F.; Rudolf, M.; Villière, T., and Villière, H.: Insulino-résistance dans le diabète, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:1086 (July 22) 1929.

13. Falta, W., and Boller, R.: Insulärer und insulinresistenter Diabetes, Klin. Wchnschr. **10**:438 (March 7) 1931.

REPORT OF CASES

CASE 1.—M. G., a woman, aged 41, admitted to the hospital on Oct. 3, 1930, had been suffering for six months from polyuria and increasing weakness and had lost much weight. She was emaciated and dehydrated. Her blood pressure was 125 systolic and 75 diastolic. The blood sugar during fasting was 235 mg. per hundred cubic centimeters, and she excreted 100 Gm. of sugar a day while on the standard diet. Forty-five units of insulin daily was required to eliminate glycosuria, and this amount was regularly required thereafter. When insulin was omitted for twenty-four hours, 135 Gm. of sugar was excreted. Her insulin tolerance was zero, any excess over 45 units causing hypoglycemic symptoms. If her original daily excretion of dextrose, 100 (Gm.), is divided by the insulin requirement, 45 (units), a dextrose equivalent of 2.2 is obtained. By the second method, the omission of insulin, the dextrose equivalent is 135 divided by 45, or 3.

This is a case of insulin-sensitive diabetes showing an immediate and quantitative response to treatment with or withdrawal of insulin.

CASE 2.—J. J., a man, aged 26, entered the hospital in coma on Dec. 7, 1932. He had been following a moderately restricted diet, and had been taking 70 units of insulin until three days before entry, when he had attempted to reduce the amount of insulin to save money. His blood sugar was 525 mg. per hundred cubic centimeters on entry. He received the usual treatment with large doses of insulin and moderately large amounts of carbohydrate and quickly recovered. The standard diet was then begun, and 90 units of insulin a day was required to keep the blood sugar within normal limits and prevent glycosuria. After two weeks on this regimen, insulin was omitted for one day. That the omission test is dangerous in such cases as this, with a marked responsiveness to insulin, is shown by the experience with this patient. During the twenty-four hours without insulin, the patient excreted 240 Gm. of sugar. The amount of urine rose from the daily average of 1,500 to 7,800 cc., and the patient lost 7 Kg. in weight. At the end of the twenty-four hours he was markedly acidotic and subcomatose, and the blood sugar was 480 mg. per hundred cubic centimeters. Insulin was then resumed, and the patient required 90 units daily as before. The insulin tolerance above 90 units was zero. The dextrose equivalent determined by the omission test was 2.6.

CASE 3.—M. R., a woman, aged 42, entered the hospital on Jan. 1, 1930. Four years before entry she had attacks of abdominal pain associated with jaundice. There had been no recurrences. For six weeks before admission she had increasing thirst and appetite, marked polyuria and rapid loss of weight. Physical examination showed slight obesity, a slightly enlarged heart and blood pressure of 175 systolic and 90 diastolic. The blood sugar during fasting was 638 mg. per hundred cubic centimeters, and the excretion of sugar on the standard diet was 120 Gm. daily. The glycosuria was eliminated, and the blood sugar brought within normal limits with 105 units of insulin a day. Before the omission test, the amount was gradually increased to 135 units, when mild hypoglycemic symptoms appeared four hours after the noon meal. On the day the insulin was omitted there was no sugar excreted. The patient remained in the hospital and did not receive any insulin; glycosuria did not recur during the next two weeks. She was discharged on the standard diet, without insulin.

The resistant element in this patient would probably have been missed in the ordinary routine examination, since the requirement of 105 units is not higher than that required in some insulin-sensitive

cases. The failure of glycosuria to recur after overdosage and subsequent omission of insulin suggests that perhaps resistance to endogenous insulin was broken, since a good carbohydrate tolerance developed, and exogenous insulin was not required. The original daily excretion of dextrose, 120 (Gm.), divided by 105 (units), the insulin requirement, gives a dextrose equivalent of 1.1. The dextrose equivalent by the second method (omission test) is zero divided by 105, or zero. Since there was no glycosuria when insulin was omitted and yet 135 units was required to cause hypoglycemic symptoms, the insulin tolerance was 135 units.

Case 4.—K. P., a woman, aged 70, entered the hospital on Oct. 1, 1932, complaining of marked weakness for two months, dryness of the mouth and cramping pains in the legs. She was fairly well nourished, had moderate general arteriosclerosis and a blood pressure of 170 systolic and 80 diastolic. Laboratory studies gave normal results, except for glycosuria and a blood sugar during fasting of 375 mg. per hundred cubic centimeters. There was no fever or other evidence of infection.

The excretion of sugar on the standard diet was 62 Gm. The insulin required was 120 units. When insulin was omitted after a control period on 120 units a day, there was only 5.7 Gm. of sugar excreted. On the day of omission, the blood sugar reached only 200 mg. per hundred cubic centimeters one hour after the noon meal. Twenty-four hours later, when the dosage of 40 units before each meal had been resumed, the blood sugar was 160 mg. per hundred cubic centimeters. As in the third case, the insulin resistance was definite, although the requirement was not exceedingly high.

Insulin was gradually increased until it reached 140 units daily, when hypoglycemic symptoms appeared. It was then gradually reduced during a period of two weeks, and finally omitted, and the patient remained aglycosuric while still on the standard diet. Six weeks later an excretion of 10 Gm. of dextrose daily appeared, which was eliminated by the reduction of the carbohydrate in the diet to 50 Gm. daily. The dextrose equivalent by the first method was 0.5 and by the second method, 0.05. The insulin tolerance may be considered as 140 units, since that amount was required to cause hypoglycemia, yet its omission was not followed by glycosuria.

Case 5.—H. P., a woman, aged 44, entered the hospital on March 18, 1930. For fifteen years she had suffered from general weakness, pruritus vulvae and furunculosis. Six years before entry, the diagnosis of diabetes was made, and she had been treated with insulin at intervals since then. For the last three years she had had attacks of precordial pain radiating down both arms.

Physical examination on entry showed marked obesity, hypertension and moderate cardiac decompensation. The heart was enlarged to the left, and there was an apical systolic murmur, a loud ringing second aortic sound and blood pressure of 178 systolic and 80 diastolic. The ankles showed considerable pitting edema. The Wassermann test of the blood was negative. The blood sugar on admission was 285 mg. per hundred cubic centimeters, and on the standard diet the excretion of sugar was 115 Gm. daily. Rapid improvement of the cardiac condition followed digitalization. The daily requirement of insulin was 120 units. An axillary abscess developed, with slight fever, and the requirement rose to 285 units, although the blood sugar during fasting at this time was only 290 mg. per hundred cubic centi-

meters. Insulin was omitted for twenty-four hours, and 112 Gm. of sugar was excreted. With more than 285 units, hypoglycemia appeared, and with less, glycosuria occurred. As the infection gradually cleared up, there was a corresponding fall in the requirement until a level of 150 units was reached. Four months later, the patient received that amount with the standard diet while being treated as an ambulatory patient, no signs of infection being present.

This case illustrates the increased resistance caused by infection in insulin-resistant diabetes. The dextrose equivalent by the first method was 0.9, and in the presence of the infection, by the omission test, was 0.4. In contrast to the patients in cases 3 and 4, who both had very high insulin tolerance, the tolerance in this case was zero.

The observations in these five cases are summarized in the table.

Analysis of Insulin Response in Five Patients with Diabetes

Name	Sex	Age, Years	Type of Diabetes	S. E. on Standard Diet*	Insulin Requirement	Insulin Before Omission	S. E. When Insulin Was Omitted	Dextrose Equivalent (1)†	Dextrose Equivalent (2)†	Insulin Tolerance	Insulin Requirement at Discharge	Comment
M. G.	F	41	Sensitive	100	45	45	135	2.2	3.0	0	45	Emaciated; B. P., 125/75
J. J.	M	26	Sensitive	...	90	90	240	...	2.6	0	90	Slender, undernourished; B. P., 120/70
M. R.	F	49	Resistant	120	105	135	0	1.1	0	135	0	Moderately obese; B. P., 175/90
K. P.	F	70	Resistant	62	120	140	5.7	0.5	0.05	140	0	Obese, arteriosclerosis; B. P., 170/80
H. P.	F	44	Resistant	115	120 (285)‡	... (285)	... (112)	0.9	... (0.4)	0	150	Obese; B. P., 178/80

* S. E. indicates sugar excretion in grams per twenty-four hours.
† Dextrose equivalent: (1) by excretion: insulin requirement ratio; (2) by omission test.
‡ Determinations in parentheses were made while the patient had an axillary abscess.

CLINICAL CHARACTERISTICS

The majority of cases of diabetes are of mixed type, showing a more or less marked insulin-resistant element. Such typical cases of resistance or sensitiveness as those described are exceptional but not rare. Falta and Boller,[13] using the methods described, and in addition the Radoslav test, found in a study of seventy-four cases, that only thirteen were of the insulin-sensitive type, while fifty-two showed a definite insulin-resistant component. Nine showed marked insulin resistance.

There are certain clinical characteristics associated with each type. Insulin sensitivity is more frequent in the younger group, and in these patients there is more tendency to emaciation, acidosis and a progressive character of the disease. The insulin requirement is smaller, the

dextrose equivalent being high (usually from 1.5 to 5 or above). Insulin tolerance is low, a slight reduction in insulin causing glycosuria and a slight excess resulting in hypoglycemia. In this type insulin acts as true substitution therapy, to which the use of thyroxin, U. S. P., in typical cases of myxedema may be compared. Priesel and Wagner [14] showed that resistance is rare in children, definite sensitivity to insulin being the rule, sometimes with a dextrose equivalent as high as 5.

The resistant type occurs chiefly in the older group, and obesity and hypertension are common. There is less tendency to emaciation, acidosis and progression in the severity of the diabetes. The insulin requirement is on the average higher, and the dextrose equivalent is low, often being only a few tenths of a gram.

On the basis of tolerance to insulin, resistant cases may be divided into two groups, one having a high tolerance (as in cases 3 and 4) and the other having a low tolerance (case 5).

CAUSES OF INSULIN RESISTANCE

Unexplained.—Studies such as those of Radoslav,[5] showing insulin resistance in the absence of explanatory factors, have been amply corroborated. Gottschalk [15] recently made similar observations. Bauer and Monguió [16] observed that the threshold value of insulin shows considerable individual variation in both diabetic and nondiabetic patients. One-tenth unit per ten kilograms of body weight sufficed to cause a fall in blood sugar in some persons, while in others 0.5 unit per kilogram was necessary. High sensitivity to insulin in vagotonic persons and low sensitivity in those showing signs of high sympathetic tone have been demonstrated by Stamm.[17]

Scott and Dotti,[18] studying standardization of insulin in rabbits, found that individual animals may be either hyposensitive or hypersensitive when their response is compared with the average response of a considerable group of animals.

The presence of some contraregulatory mechanism which may be hyperactive in certain people seems necessary to explain insulin resistance such as that described in the cases reported here. The antagonism

14. Priesel, R., and Wagner, R.: Treatment of Diabetes Mellitus in Childhood, Leipzig, Georg Thieme, 1932.

15. Gottschalk, A.: Der Angriffspunkt der Kohlehydrate bei ihrer antiketogenischen Wirkung, Zentralbl. f. inn. Med. **53**:776 (May 14) 1932.

16. Bauer, J., and Monguió, J.: Ueber den Schwellenwert des Insulins, Ztschr. f. klin. Med. **121**:476, 1932.

17. Stamm, E.: Die Insulinempfindlichkeit des nichtdiabetischen Menschen und ihre Beziehung zum vegetativen Nervensystem, Arch. f. Verdauungskr. **48**:104 (Aug.) 1930.

18. Scott, E. L., and Dotti, L. B.: Insulin Dosage and Blood Sugar Changes, Arch. Int. Med. **50**:511 (Oct.) 1932.

between insulin and the suprarenal-sympathetic system is easily demonstrable, and suggests that hyperactivity or hypersensitivity of this system may be a factor in the resistance. Simultaneous injections of epinephrine and insulin show antagonistic effects on the blood sugar. Patients with Addison's disease exhibit hypoglycemia and marked sensitivity to insulin. Postinsulin hypoglycemia is counteracted by injections of epinephrine. Clinically, the symptoms of hypoglycemia closely resemble those following an overdose of epinephrine: trembling, nervousness and sweating. Cannon [19] demonstrated that an increased secretion by the suprarenal medulla accompanies recovery from hypoglycemia.

Dworkin [20] found that bilateral extirpation of the sympathetic nerve chain renders cats permanently hypersensitive to insulin. De Takáts and Cuthbert [21] noted a rise in sugar tolerance in dogs, with increased susceptibility to insulin after celiac ganglionectomy, presumably due to reduction in the insulin-antagonistic activity of the suprarenal-sympathetic system. Observation of the islands of Langerhans in vivo [22] has revealed constriction of the arterioles supplying the islands after intravenous injections of epinephrine or solution of pituitary. Colwell and Bright,[23] after demonstrating that dextrose combustion in cats can be suppressed by the continuous administration of epinephrine, concluded that ordinary diabetes mellitus may be a functional disorder of the pancreas depending on a disease of the sympathetic nervous system in which an increased secretion of epinephrine is a factor.

Despite the absence of definite proof that clinical insulin resistance is associated with hyperactivity of the suprarenal-sympathetic system, such strongly suggestive clinical and experimental evidence makes it highly probable that this is the explanation for the common type of relative resistance which I have described.

In many instances, a poor response of the blood sugar to insulin can be attributed to some complication. Such cases can be grouped as follows:

Infection.—Infections complicating diabetes usually necessitate increased dosage of insulin. The mechanism producing this relative

19. Cannon, W. B.; MacIver, M. A., and Bliss, S. W.: Studies on Conditions of Activity in Endocrine Glands, Am. J. Physiol. **69**:46 (June) 1924.

20. Dworkin, S.: The Response of Sympathectomized Animals to Insulin, Am. J. Physiol. **98**:467 (Oct.) 1931.

21. de Takáts, G., and Cuthbert, F. P.: Effect of Celiac Ganglionectomy on Sugar Tolerance in Dogs, Am. J. Physiol. **102**:614 (Dec.) 1932.

22. Berg, B. N.: A Study of the Islands of Langerhans in Vivo with Observations on the Circulation, Am. J. Physiol. **95**:186 (Oct.) 1930.

23. Colwell, W. B., and Bright, E. M.: Suppression of Glucose Combustion by Continuous Prolonged Epinephrin Administration, Am. J. Physiol. **92**:555 (April) 1930.

resistance is as yet obscure. Williams and Dick [24] recently found glycosuria and lowered carbohydrate tolerance in 41 per cent of one hundred and eight nondiabetic patients with acute infectious diseases. They attributed the loss of tolerance to damage to the pancreas. Schwentker and Noel [25] studied the carbohydrate metabolism in children with diphtheria and in rabbits given diphtheria toxin and concluded that there is increased glycogenolysis, followed by decreased glycogenesis, owing to the suppression of the endogenous production of insulin.

Lawrence and Buckley [26] noted inhibition of the action of insulin by diphtheria toxin in rabbits. At necropsy there were signs of overactivity in the thyroid and suprarenal glands. Depisch and Hasenöhrl [27] found that when pus from metastatic abscesses or blood serum from persons with diabetes with infection was mixed with insulin, its power to lower blood sugar decreased. Subcutaneous injections of trypsin were found by Buckley [28] to produce insulin resistance in rabbits.

Thus, three types of explanation have been offered: toxic injury to the pancreatic islets, production of hormones antagonistic to insulin and neutralization or destruction of insulin by toxins or ferments circulating in the blood.

Hyperthyroidism.—Insulin-resistant diabetes in the presence of hyperthyroidism was first described by Rosenberg and Meyer,[29] Strauss [30] and Kogan.[31] Since then such cases have been reported frequently. Hyperthyroidism seems to work in two ways to cause insulin resistance: The liver is made more responsive to glycogenolytic impulses, the blood sugar rising and the liver glycogen becoming depleted. In addition, glycogenesis is inhibited, so that the removal of sugar from the blood is interfered with, and storage of glycogen in the

24. Williams, J. L., and Dick, G. F.: Decreased Dextrose Tolerance in Acute Infectious Diseases, Arch. Int. Med. **50**:801 (Dec.) 1932.

25. Schwentker, F. F., and Noel, W. W.: Carbohydrate Metabolism in Diphtheria Intoxication, Bull. Johns Hopkins Hosp. **46**:259 (April) 1930.

26. Lawrence, R. D., and Buckley, O. B.: Inhibition of Insulin Action by Toxemias and Its Explanation, Brit. J. Exper. Path. **8**:58 (Feb.) 1927.

27. Depisch, F., and Hasenöhrl, R.: Experimentelle Untersuchungen über die Insulinresistenz beim Diabetes mellitus, Ztschr. f. d. ges. exper. Med. **58**:110, 1927.

28. Buckley, O. B.: Effect of Subcutaneous Injections of Trypsin on the Blood Sugar and on Insulin Action, Brit. J. Exper. Path. **12**:13 (Feb.) 1931.

29. Rosenberg, M., and Meyer, W. B.: Klinischer Beitrag zur Pathogenese des extrainsulären "Diabetes," Deutsche med. Wchnschr. **5**:935 (June 5) 1925.

30. Strauss, H.: Ueber insulin-resistente Diabetiker, Klin. Wchnschr. **4**:491 (March 12) 1925.

31. Kogan, V.: Antagonismus und Korrelation zwischen Pankreas, Nebennieren und Hypophysis, Ztschr. f. klin. Med. **104**:457, 1926.

liver is much diminished. Pettavel,[32] and Wegelin [33] found livers absolutely devoid of glycogen in exophthalmic goiter.

Serio [34] described the disappearance of insulin resistance in a patient with diabetes after relief from hyperthyroidism. Zeckwer,[35] studying spontaneous resistance in rabbits, found that in two animals with marked spontaneous resistance, thyroidectomy increased the response to insulin from ten to fifteen times.

Pituitary Disorders.—Early in the insulin era patients with complicating pituitary disease were found to respond poorly to treatment. Falta,[4] Mahler and Pasterny,[2] Mauriac and Aubertin,[36] and Wemyss [37] described such cases. Disorders supposed to be associated with hypersecretion of the anterior lobe are frequently accompanied by hyperglycemia. Cushing and Davidoff [38] found glycosuria in one fourth of a series of a hundred persons with acromegaly. In eleven of forty-four collected cases which came to autopsy the patient died in diabetic coma. Cammidge,[39] Joslin,[40] and Labbé, Escalier and Dreyfus [41] described the insulin-resistant type of diabetes associated with acromegaly. In a case of Cushing and Davidoff, removal of a pituitary tumor caused disappearance of hyperglycemia and glycosuria.

Further confirmation of the rôle of the anterior pituitary lobe is given by many recent investigations. As hypersecretion causes less response, so hyposecretion causes exaggerated response to insulin. A patient with hypophyseal cachexia, whose case was reported by Lucke,[42] showed marked hypersensitivity. Houssay and Magenta [43]

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32. Pettavel, C. A.: Weiterer Beitrag zur pathologischen Anatomie des Morbus Basedowii, Mitt. a. d. Grenzgeb, d. Med. u. Chir. **27**:694, 1914.

33. Wegelin, C.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 402.

34. Serio, F.: Zur Kenntnis des insulinresistenten Diabetes, Klin. Wchnschr. **10**:1998 (Oct. 24) 1931.

35. Zeckwer, I. T.: Spontaneous Insulin Resistance in Rabbits, Am. J. M. Sc. **182**:153 (Sept.) 1931.

36. Mauriac, P., and Aubertin, E.: Insulino-résistances et diabètes par neutralisation, Presse méd. **34**:1633 (Dec. 29) 1926.

37. Wemyss, H. L. W.: Diabetes Complicating Acromegaly, and Pituitrin-Insulin Antagonism, Edinburgh M. J. **34**:343 (June) 1927.

38. Cushing, H., and Davidoff, L. M.: Pathological Findings in Four Cases of Acromegaly, with a Discussion of Their Significance, Monograph of Rockefeller Institute for Medical Research, 1927, no. 22, p. 89.

39. Cammidge, P. J.: Pituitary Glycosuria, Proc. Roy. Soc. Med. (Sect. Med.) **19**:37 (Sept.) 1926.

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41. Labbé, M.; Escalier, A., and Dreyfus, G.: Acromégalie et diabète, Ann. de méd. **29**:222 (March) 1931.

42. Lucke, H.: Hypophysäre Magersucht und Insulin, Klin. Wchnschr. **11**: 1988 (Nov. 26) 1932.

43. Houssay, B. A., and Magenta, M. A.: Sensitivity to Insulin After Hypophysectomy, Rev. Asoc. méd. argent. (Soc. de biol.) **37**:389, 1924.

and Olmsted and Logan [44] found that hypoglycemia was much more easily provoked in animals after hypophysectomy. Falta and Högler [45] found that injections of anterior pituitary extract in man prevented hypoglycemia following insulin. That the resistance caused by the anterior pituitary lobe may operate in a manner similar to that suggested for the thyroid is indicated by the work of Eitel and Loeser.[46] They found that injections of the anterior pituitary thyrotropic hormone into guinea-pigs caused hyperthyroidism and depletion of the glycogen in the liver.

Injections of posterior lobe extract also cause insulin resistance in man, as shown by Burn [47] and Blotner and Fitz.[48]

Suprarenal Glands.—The probable rôle of the suprarenal-sympathetic system in so-called "unexplained insulin resistance" has been discussed. It is probable, also, that this system is concerned in the resistance of hyperthyroidism, pituitary disorders and infections. These disorders may be accompanied by increased blood sugar and depleted glycogen in the liver, as would be expected with increased secretion of epinephrine. The frequent occurrence of vascular hypertonia in insulin resistance also supports this theory.

Hepatic Disorders.—Leech,[49] Widal and co-workers,[50] Labbé [51] and Chabrol and Hébert [52] described cases in which disproportionately large doses of insulin were required in the presence of various hepatic disorders. In such cases it is probable that the resistance depends at least partly on the loss of the glycogenic function of the liver. Diminished tolerance to dextrose follows the reduction of glycogen in the liver.[53]

44. Olmsted, J. M. D., and Logan, H. D.: Effect of Insulin on Central Nervous System and Its Relation to Pituitary Body, Am. J. Physiol. **66**:437 (Oct.) 1923.

45. Falta, W., and Högler, F.: Ueber das Hypophysenvorderlappenhormon, Klin. Wchnschr. **9**:1807 (Sept. 27) 1930.

46. Eitel, H., and Loeser, A.: Beziehungen zwischen Hypophysenvorderlappen, Schilddrüse, und Kohlehydratstoffwechsel der Leber, Klin. Wchnschr. **11**:1669 (Oct. 1) 1932.

47. Burn, J. H.: Modification of Action of Insulin by Pituitary Extract and Other Substances, J. Physiol. **57**:318 (June) 1923.

48. Blotner, H., and Fitz, R.: Effect of Insulin, Pituitrin and Adrenalin upon Blood Sugar Level, J. Clin. Investigation **5**:51 (Dec.) 1927.

49. Leech, E. B.: Bronzed Diabetes: Its Reactions to Dietetic and Insulin Treatment, Lancet **2**:69 (July 14) 1923.

50. Widal, F.; Abrami, P.; Weill, A., and Laudat: Action dissociée de l'insuline sur la glycosurie et l'acétonurie, Presse méd. **32**:253 (March 22) 1924.

51. Labbé, M.: Coma hépatique chez un diabétique acidosique, Bull. et mém. Soc. méd. d. hôp. de Paris **48**:1560 (Nov. 14) 1924.

52. Chabrol, E., and Hébert, P.: Paris méd. **1**:453 (May 16) 1925.

53. Staub, H.: Untersuchungen über den Zuckerstoffwechsel des Menschen, Ztschr. f. klin. Med. **93**:89 (Jan.) 1922.

Himsworth [54] suggested that a hepatic ferment necessary to activate insulin is reduced in hepatic diseases. Boller and Uberrack [55] recently showed that enormous doses of insulin are often tolerated by patients having parenchymatous damage to the liver.

Hemochromatosis.—This disease, in which deposits of pigment in the liver and the pancreas may be marked, is frequently accompanied by insulin-resistant diabetes. Widal, Abrami, Weill and Laudat [56] were the first to record this association. Sheldon [56] found that with progressive deposit of pigment in the pancreas there is increasing severity of the diabetes. The patient of Allan and Constam [57] required 500 units to eliminate glycosuria, while Root's patient [11] required over 1,600 units daily shortly before death. In Stetson and Peter's case,[58] increasing glycosuria persisted despite rising doses of insulin. In hemochromatosis a diminished production of insulin and interference with the formation and storage of glycogen by the liver and muscles apparently cause the insulin resistance.

Diseases of the Pancreas.—Pathologic studies of the pancreas in ordinary diabetes have failed to demonstrate constant lesions, as shown by Warren.[59] However, in acute pancreatic disorders diabetes frequently develops.[60] Glycosuria may develop in cases of pancreatic malignancy. Preexistent diabetes becomes more severe, but in the absence of other complications, the response to exogenous insulin is good. There is, in other words, no true insulin resistance. Increasing doses of insulin are required because of diminished production of insulin. Root [11] described pancreatic carcinoma occurring in a patient with previously mild diabetes, increasing doses up to 100 units daily being required.

Miscellaneous Conditions.—In acidosis and coma large doses of insulin may temporarily be required. However, after proper treatment this apparent resistance promptly disappears. Umber and Rosen-

54. Himsworth, H. P.: The Activation of Insulin, Lancet **2**:935 (Oct. 29) 1932.

55. Boller, R., and Uberrack, K.: Die Insulintoleranz bei Fällen von Ikterus, Klin. Wchnschr. **11**:671 (April 16) 1932.

56. Sheldon, J. H.: Iron Content of Tissues in Hemochromatosis, Quart. J. Med. **21**:123 (Oct.) 1927.

57. Allan, F. N., and Constam, G. R.: Insulin Resistance in a Case of Bronze Diabetes, M. Clin. North America **12**:1677 (May) 1929.

58. Stetson, R. P., and Peters, J. P.: Carbohydrate Metabolism in a Case of Hemochromatosis, Arch. Int. Med. **50**:226 (Aug.) 1932.

59. Warren, S.: Pathology of Pancreas in Nondiabetic Persons, Arch. Int. Med. **44**:663 (Nov.) 1929.

60. Bernhard, F.: Das Auftreten des Diabetes mellitus nach akuten Pankreaserkrankungen, Klin. Wchnschr. **10**:632 (April 4) 1931.

berg [61] considered all cases of renal glycosuria refractory because of the failure of the glycosuria to disappear under treatment with insulin. This is obviously a wrong use of the term, since in renal glycosuria the response of the blood sugar to insulin is normal. Cutaneous diseases may be associated with resistance to insulin, which perhaps depends on the loss of the skin as a glycogen depot. The greater carbohydrate tolerance with exercise is a matter of common observation. Conversely, a diabetic patient confined to bed will often rapidly lose tolerance. During cardiac decompensation large doses may temporarily be required, owing, perhaps, to poor absorption of insulin in the presence of edema or to congestion of the liver.

COMMENT

The practical advantages of distinguishing insulin-sensitive and insulin-resistant cases would seem to be numerous. In some cases, the discovery of resistance might lead to a search for, and disclosure of, an explanatory complicating factor. A better understanding of the metabolic disturbance in each case would result, making possible a more intelligent adjustment of diet and insulin. In certain cases it has been shown that the response to alterations in the diet is very different in the two types. Fat may be considerably increased in insulin-sensitive cases without an increase in the excretion of dextrose, while increased fat in the resistant type may lead to a decrease in the dextrose tolerance. Carbohydrate, on the other hand, may be considerably increased in many resistant cases without increased excretion of sugar, while in the sensitive cases larger amounts of carbohydrate immediately lead to glycosuria. [62] Schmidt [63] distinguishes "sthenic" from "asthenic" diabetes, the two groups corresponding roughly to those described as insulin-resistant and insulin-sensitive. He has shown that the dietary management should be different in the two types. Observations such as the foregoing demonstrate the fallacy of using standard general dietary formulas in all types of diabetes. Determination of the relative response of each patient to insulin should allow a better individual planning of the diet.

A large field for the combined clinical and pathologic study of diabetes is opened by the demonstration of the frequency of relative insulin resistance in uncomplicated cases. The insulin-sensitive or

61. Umber, F., and Rosenberg, M.: Ueber Insulinrefraktäre Zuckerausscheidungen und Klassifikation des Diabetes auf Grund seines Verhaltens gegenüber Insulin, Klin. Wchnschr. **4**:583 (March 26) 1925.

62. Falta, W., and Boller, R.: Ueber das Glucose-Aequivalent des Insulins, Wien. med. Wchnschr. **82**:1296 (Oct. 8) 1932.

63. Schmidt, R.: Klinik des "sthenischen" Ueberdruckdiabetes, Klin. Wchnschr. **9**:1969 (Oct. 18) 1930.

"insular" type is apparently due primarily to decreased production of insulin. Insulin resistance seems to depend on a contraregulatory factor which counteracts the effect of insulin in the body. The possibility of a pure insulin-resistant diabetes is suggested, depending entirely on increased contraregulation, possibly by the suprarenal-sympathetic system, the pancreas being normal.

Studies such as those of Warren,[59] who has demonstrated that any lesions found in the diabetic pancreas can be duplicated in the nondiabetic pancreas, lend support to the theory of the extrapancreatic origin of some cases of diabetes. If careful clinical observations of the responsiveness to insulin in each case were correlated with pathologic changes in the future, much light might be thrown on this subject.

SUMMARY

1. Attention is called to the frequency of occurrence of relative resistance to insulin in uncomplicated cases of diabetes mellitus.

2. Clinical studies of two cases of insulin-sensitive and three cases of insulin-resistant diabetes are reported.

3. In two of these patients resistance to endogenous insulin was apparently broken, an overdosage of insulin being followed by marked improvement in carbohydrate tolerance.

4. The clinical characteristics of the insulin-resistant type as distinguished from the insulin-sensitive type are outlined.

5. Reported cases of insulin resistance may be grouped as follows:

(*a*) Unexplained, such as the five cases reported in this paper. Insulin resistance is usually of mild or moderate degree in this group. Hyperactivity of the suprarenal-sympathetic system is suggested as the cause of this type of resistance. Many of these patients might be termed constitutionally resistant.

(*b*) Infection.

(*c*) Destructive pancreatic disease.

(*d*) Disorders of other endocrine glands, particularly the thyroid, pituitary and suprarenal glands.

(*e*) Hepatic disorders.

(*f*) Miscellaneous conditions such as acidosis, coma, diseases of the skin and cardiac decompensation.

6. The value of determining the relative responsiveness to insulin for treatment as well as for further study of diabetes is emphasized.

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SKIN LESIONS OF PELLAGRA

AN EXPERIMENTAL STUDY

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Nearly two hundred years ago pellagra was described as a clinical syndrome related to poverty and inadequate nutrition.[1] Goldberger and his associates[2] were able to prevent, to produce and to cure the disease by varying certain constituents in a diet administered to human beings. They finally considered the lack of vitamin B_2 (G), the so-called "anti-dermatitis factor," as the sole cause of the disease. At the present time some investigators[3] do not accept that claim, advancing the theory that a predisposing dietary lack is important in the pathogenesis of pellagra, but that a precipitating element is also necessary. I[4] reported in a previous publication that the cutaneous lesions of persons with pellagra improved while the patients were restricted to a so-called "pellagra-producing" diet. Since this diet consisted of such diverse foods as cornmeal, pork fat, artificially colored (synthetic) maple syrup, polished rice, corn-starch pudding and sugar, it seemed advisable to observe the cutaneous lesions of the patients limited to a diet less complex in food materials and even more deficient in vitamin B_2 (G).

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1. Casal, D. G.: Historia natural y medica de el Principado de Asturias, Abra posthuma del Doctor D. G. Casal, Medico de Su Magnestad y su Proto-medicin de Castilla, Madrid, 1762.

2. Goldberger, J.; Waring, C. H., and Willets, D. G.: The Prevention of Pellagra, Pub. Health Rep. **30**:3116, 1915. Goldberger, J.; Wheeler, G. A., and Sydenstricker, E.: A Study of the Relation of Diet to Pellagra Incidence, Pub. Health Rep. **35**:648, 1920. Goldberger, J., and Wheeler, G. A.: Experimental Production of Pellagra in Human Beings by Means of Diet, U. S. Pub. Health Service, Hyg. Lab., Bull. no. 120, 1920.

3. Aykroyd, W. R.: Vitamin B_2 Content of Cereals and Supposed Connection Between Human Pellagra and Deficiency of This Vitamin, Biochem. J. **24**:1479, 1930. Gurin, S. S., and Eddy, W. H.: Is Rat Dermatitis Consequent on Vitamin B_2 (G) Deficiency True Pellagra? J. Exper. Med. **54**:421, 1931.

4. Spies, T. D.: Pellagra: Improvement While Taking So-Called "Pellagra-Producing" Diet, Am. J. M. Sc. **184**:837, 1932.

Evidence is presented in this paper to show that the dermatitis of pellagra often improves while the patient is restricted to a diet of corn-starch and lactose.

EXPERIMENTAL WORK

Materials and Methods.—Ten patients with the characteristic dermatitis of pellagra were chosen for this experiment, and extreme care was exercised to select those without neurologic involvement. Each patient remained in bed throughout the experiment and was given a diet of corn-starch and lactose amounting to 2,000 or 3,000 calories a day. Two of the six persons in this series having stomatitis were unable to tolerate this diet and frequently vomited; the stomatitis and glossitis rapidly became worse; so the diet was discontinued. As soon as the dermatitis of the eight remaining patients healed, they were given a high caloric, high vitamin diet. In order to test this diet still further it was fed to six young albino rats.

Observations.—The skin lesions of the eight patients who tolerated the diet of lactose and corn-starch showed definite improvement during the first six to fifteen days of the experiment. In all respects the healing process appeared similar to that of persons with pellagra receiving an adequate diet. Each patient rapidly lost weight and strength during the experimental period, but this apparently did not affect the steady improvement of the dermatitis. The stomatitis of one person improved, and that of the three others became worse while they received the restricted diet. The four patients free from stomatitis at the beginning of the experiment did not develop it, and none of the patients in this experiment showed any signs of involvement of the central nervous system. The two patients who were unable to tolerate the corn-starch and lactose rapidly improved after the experimental diet was discontinued and a well rounded one substituted. The rats receiving the lactose and corn-starch lost weight and died within four weeks after the beginning of the experiment.

COMMENT

It has been shown that the cutaneous lesions of patients with pellagra improved while they were receiving a diet of corn-starch and lactose. This work confirms and somewhat extends my previous observation that persons with pellagra restricted to a diet of polished rice, corn-starch, corn-meal, pork fat, maple syrup and sugar showed marked improvement of their dermatitis. The previous "pellagra-producing" diet [5] and the foods used in this experiment were found inadequate for the normal nutrition of young rats. It is impossible to state whether or not the dermatitis would have recurred had the patients been restricted to either of these nonpalatable diets for an indefinite period. A satisfactory explanation for the striking improvement of the dermatitis is difficult to offer. Rest in bed may have been a contributing factor, or there may have been more essential elements in this deficient diet than in the insignificant amount of food ingested by these patients before enter-

5. Spies, T. D., and Grant, Jean: An Experimental Study of a So-Called "Pellagra-Producing" Diet, Am. J. Physiol. **104**:18, 1933.

ing the hospital. Possibly these patients had begun to improve, although there was no evidence of it at the time they were first given the restricted diet. Wheeler [6] has suggested that the improvement of the patients receiving an inadequate diet may take place as a result of a breakdown in the body protein with subsequent healing of the lesions. It is true that each person on this restricted diet showed a loss of body weight, but without exception each had a definite history of marked loss in weight, yet with no healing of the lesions, before he was admitted to the hospital.

I,[7] as well as many others, have noted that the disease may involve the central nervous system, the gastro-intestinal tract and the skin in the same patient while in other patients it may affect one or two organ systems. In several instances [7] I have observed that the dermatitis and stomatitis healed while there was steady progression of the disease of the central nervous system. It can be seen from this experiment that too much importance may have been attached to the healing of the cutaneous lesions by some of the investigators of the past. In view of this work and of the known observations concerning the lack of uniformity of the disease in involving the various organ systems of the body, it even appears possible that the specific chemical substance related to the development of dermatitis is not the same as that affecting the other manifestations of pellagra.

SUMMARY AND CONCLUSIONS

1. It has been shown in this experiment that persons with pellagra tolerating a diet of lactose and corn-starch show improvement of their cutaneous lesions. This work confirms and somewhat extends my previous observation that the dermatitis of pellagra improves while the patients receive a so-called "pellagra-producing" diet.

2. It is recommended that improvement in dermatitis be interpreted with great care before accepting it either as an index of efficacious treatment or of favorable prognosis.

3. It appears possible that the specific chemical substance related to the development of the dermatitis is not the same as that affecting manifestations of the disease in the gastro-intestinal or central nervous system.

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6. Wheeler, G. A.: Results of Some Studies Dealing with Diets in Pellagra (Discussion), South. Med. & Surg. **94**:131, 1932.

7. Spies, T. D.: Unpublished data.

CHANGES IN BLOOD PRESSURE OF YOUNG MEN OVER A SEVEN YEAR PERIOD

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In 1925, Sutherland and one of us (Dr. Diehl)[1] published an analysis of the systolic blood pressures of 5,122 male students of the University of Minnesota. The study showed that although most college students give normal blood pressure readings at all times, some have systolic pressures which are persistently above 140 mm.; others, systolic pressures persistently between 130 and 140 mm.; others, pressures intermittently above 130 mm.; and still others, pressures above 130 mm. on only one occasion. The significance of these moderate, intermittent and transient elevations of blood pressure in young persons was discussed at that time, but it was concluded that only follow-up studies over many years could finally determine whether these were unimportant or whether they represented an early stage of persistent hypertension.

We are now reporting the first of a series of follow-up studies of blood pressure in college students. In this study determinations of blood pressure were made on 155 young men all of whom had been students at the University of Minnesota from five to ten years previously. The average age of these young men at the time of their first physical examination in the university was 19.8 years, and at the time of the follow-up examination, 26.8 years. This indicates an average interval of seven years between examinations. While in college each of the men had had at least two determinations of blood pressure, and the group as a whole had averaged four determinations, all of which were made by physicians on the staff of the Students' Health Service. The follow-up examination, which usually consisted of only one determination, was made either by a member of the staff of the Health Service or by a physician in private practice.

The average of the systolic pressures of these 155 undergraduates was 126.18 ± 0.78 mm. At the time of the follow-up examination seven years later, the average was 123.97 ± 0.57 mm. Although the

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1. Diehl, H. S., and Sutherland, K. H.: Systolic Blood Pressures in Young Men, Arch. Int. Med. **36**:151 (Aug.) 1925.

probable errors indicate that the apparent decrease in the mean pressures of the group is without significance, it is at least interesting to note that the average pressure showed no increase over this period.

DIVISION INTO GROUPS

For purposes of analysis the 155 subjects were divided into five groups according to their blood pressures while in college. These groups are as follows: group I, called the persistent hypertension group, composed of persons whose systolic pressures averaged 140 mm. or more; group II, called the group with moderately elevated pressures, composed of persons whose systolic pressures averaged between 130 and 140 mm.; group III, called the group with intermittently elevated pressures, composed of persons who had systolic pressures intermittently above 130 mm.; group IV, called the group with transiently elevated pressure, composed of those who gave only one reading above 130 mm., and

TABLE 1.—*Average Ages and Systolic Pressures by Groups*

	During College Years		From Five to Ten Years Later	
	Average Age	Average Systolic Pressure	Average Age	Average Systolic Pressure
Group I	21.71 ± 0.87	144.63 ± 1.48	29.00 ± 0.80	138.27 ± 1.48
Group II	19.44 ± 0.40	133.63 ± 1.58	27.19 ± 0.43	128.75 ± 1.47
Group III	18.71 ± 0.38	128.82 ± 0.72	27.39 ± 0.51	126.75 ± 0.51
Group IV	20.67 ± 0.37	124.35 ± 0.85	27.23 ± 0.31	124.89 ± 0.89
Group V	21.21 ± 0.44	116.13 ± 0.52	28.10 ± 0.39	116.84 ± 0.62

group V, called the normal group, composed of those whose systolic pressures were always under 130 mm.

Obviously these groupings are arbitrary and a subject's classification into one or another might change with an increase in the number of determinations which were made. However, for the purposes of this study these groupings will serve reasonably well.

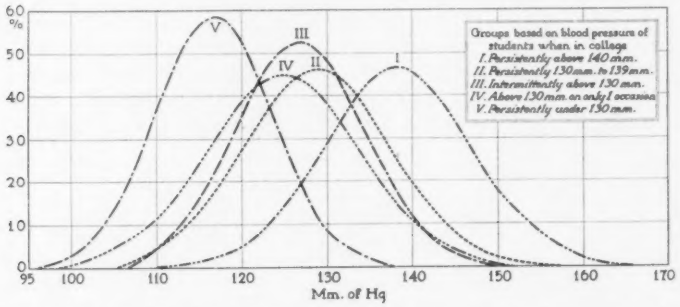
OBSERVATIONS

Age.—Table 1 shows the average ages of the groups both at the time of the original examinations and at the time of the follow-up examinations. Although the group with persistent hypertension (I) shows the highest average age and the normal group (V) the next highest average age, none of the differences in age are statistically significant.

Group with Persistent Hypertension.—In this group there were 15 students each of whom showed an average systolic pressure of 140 mm. or more during the years at college. Seven years later, 12, or 80 per

cent,[2] of these students had systolic pressures of 130 mm. or more; 8, or 53 per cent,[2] pressures of 140 mm. or more, and 3, or 20 per cent,[2] pressures of 160 mm. or more. The average pressure of the group, however, decreased from 146.63 ± 1.48 mm. during the years at college to 138.37 ± 1.48 mm. at the time of the follow-up study. This decrease in the average of the group is due to the fact that 3 of the men who had had a systolic pressure of 140 mm. in college gave readings of less than 130 mm. at the time of the follow-up examination.

Palmer[3] found in a follow-up study of 49 Harvard students who had systolic pressures of 140 mm. or more when in college that after ten years 22 per cent had pressures of over 140 mm. and 10 per cent had pressures of over 150 mm. This lower incidence of persistently high pressures in Palmer's series than in ours—22 per cent as compared to 53 per cent—is doubtless due largely to differences in the composition



Theoretical normal distribution curves of the systolic blood pressures of the several groups at the time of the follow-up study.

of the groups in which the follow-up studies were made, Palmer's hypertension group being so designated on the basis of a single physical examination in college, whereas our hypertension group contained only students whose systolic pressures in college averaged 140 mm. or more on repeated examinations.

Group with Moderately Elevated Pressures.—Eight, or 50 per cent of the 16 men who had systolic pressures of from 130 to 139 mm. during college years still had pressures of 130 mm. or more, and 2, or 12.5 per cent, had pressures of 140 mm. or more, seven years later. The average pressure of this group during the years at college was

2. Percentages such as these are used throughout in order to show trends. If they are to be used for other purposes, the small number of the cases on which they are based needs to be taken into consideration.

3. Palmer, Robert Sterling: The Significance of Essential Hypertension in Young Male Adults, J. A. M. A. **94**:694 (March) 1930.

133.63 ± 1.58 mm., and at the time of the follow-up examination, 128.75 ± 1.47 mm.

Group with Intermittently Elevated Pressures—This group consisted of 24 students whose systolic blood pressures during college years were intermittently above 130 mm. At the time of the follow-up examination 9, or 37 per cent, of the students had systolic pressures of 130 mm. or more, and 2, or 8 per cent, pressures of 140 mm. or more. The average systolic pressure of the group when in college was 128.82 ± 0.72 mm., and at the time of the follow-up examination, 126.75 ± 0.56 mm.

Group with Transient Elevations of Blood Pressure.—This group consisted of 45 students, each of whom during college years showed a systolic blood pressure reading of 130 mm. or more on only one occasion. Seven years later, 13, or 30 per cent, of these students had systolic pressures of 130 mm. or more, and 2, or 5 per cent, pressures of 140 mm. or more. The average systolic pressure of these persons during their college years was 124.35 ± 0.85 mm., and at the time of the follow-up examination, 124.89 ± 0.89 mm.

Normal Group.—Fifty-five men whose systolic blood pressure during their undergraduate years was always below 130 mm. were reexamined, and only 2, or 4 per cent, of them had pressures of over 130 mm.; none had a pressure as high as 140 mm. Palmer reports that in 66 Harvard men whose blood pressures had been normal when in college reexamination after ten years revealed that 4.5 per cent had systolic pressures between 140 and 150 mm., and that 1 had a pressure of over 150 mm. Here again the differences between our results and Palmer's are doubtless due to differences in the composition of the groups studied, or, to be more specific, to different definitions of "normal."

COMMENT

Various studies of blood pressure have indicated that most of the elevations observed in young persons are transient and are due largely to nervousness and excitement at the time of examination. Whether these transient or recurrent elevations of blood pressure produce strain on the cardiovascular system which eventually leads to persistent hypertension is an important question and one on which there has been much difference of opinion. The results of this study indicate that young men who show persistent, intermittent or even transient elevations of blood pressure during their college years are much more likely to have elevated pressures after a period of from five to ten years than those in whom the blood pressure was consistently normal while they were in college. Apparently also the probability of their having elevated blood

pressures in later years is in direct proportion to the frequency with which their pressures were elevated while in college.

Table 2 gives the systolic pressures of the several groups at the time of the follow-up study, and the chart shows the theoretical normal distribution curves which can be drawn from them. The actual distribution curves of these data are somewhat irregular and slightly skewed, but the theoretical curves are more easily followed and for comparative purposes are quite satisfactory. The differences in the pressures of the several groups at the time of the follow-up study are clearly shown by the areas of these curves above or below the various points on the millimeter scale. Each of the curves is significantly different from the others, and the percentage of overlapping between curves I and V is only 18.6 per cent.

TABLE 2.—*Systolic Blood Pressures After from Five to Ten Years*

		Systolic Pressures on Follow-Up Study							
		100 to 119 Mm.		120 to 129 Mm.		130 to 139 Mm.		140 Mm. or More	
Groups Based on Blood Pressures While in College	Total Number of Cases	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
I. Persistent hypertension...	15	0	0	3	20	4	27	8	53
II. Moderate elevation.....	16	2	12	6	37	6	37	2	12
III. Intermittent elevation.....	24	2	8	13	54	7	29	2	8
IV. Transient elevation.....	45	15	33	17	37	11	25	2	5
V. Normal.....	55	36	70	17	31	2	4	0	0

In the terms of probability the results of this study would be stated as follows: (1) If a young man's systolic blood pressure in college is persistently above 140 mm., the chances are slightly more than 1 in 2 that it will be 140 mm. or more, and about 4 in 5 that it will be 130 mm. or more seven years later; (2) if his systolic pressure in college averages between 130 mm. and 140 mm., the chances are about 1 in 8 that it will be above 140 mm. and about 1 in 2 that it will be above 130 mm. seven years later; (3) if during the years at college his pressure is intermittently above 130 mm., the chances are 1 in 12 that it will be above 140 mm. and slightly more than 1 in 3 that it will be above 130 mm. seven years later; (4) if during his college years his systolic pressure is found to be above 130 mm. on only one occasion, there is about 1 chance in 20 that it will be above 140 mm. and about 1 in 4 that it will be above 130 mm. seven years later; and (5) if his systolic pressure during his college years is always under 130 mm., there is less than 1 chance in 100 that it will be above 140 mm. and only about 1 in 25 that it will be above 130 mm. seven years later.

SUMMARY

1. A five to ten year follow-up study of systolic blood pressure in 155 young men is reported.

2. The average age of the young men at the time of the original examinations was 19.8 years, and at the time of the follow-up examination, 26.8 years.

3. The average systolic pressure of the group during the years at college was 126.18 ± 0.78 mm. and at the time of the follow-up examination, 123.97 ± 0.57 mm.

4. For purposes of comparison the group was divided on the basis of blood pressure records when in college into five subgroups as follows: (1) persistently elevated pressures; (2) moderately elevated pressures; (3) intermittently elevated pressures; (4) transiently elevated pressures, and (5) normal pressures.

5. At the time of the follow-up study the incidence of systolic pressures of 130 mm. or more in the several groups was as follows: group I, 80 per cent; group II, 50 per cent; group III, 37 per cent; group IV, 30 per cent, and group V, 4 per cent.

6. At the same time the incidence of systolic pressures of 140 mm. or more was as follows: group I, 53 per cent; group II, 12 per cent; group III, 8 per cent; group IV, 5 per cent, and group V, none.

7. At the time of the follow-up study only 2 persons showed blood pressures of over 160 mm., and both of these belonged to group I.

8. Although the number of cases in certain of the groups is small, the "chi square test" indicates that the possibilities of the differences between consecutive groups shown in table 2 being due to chance are as follows: between groups I and II, 8 in 100; between groups II and III, 42 in 100; between groups III and IV, 14 in 100, and between groups IV and V, 3 in 100.

9. These results apparently indicate that young men who show elevations of blood pressure, even though these are transient, are more likely to have high blood pressure after from five to ten years than men whose blood pressure at the earlier ages was consistently within so-called normal limits, and that the greater the degree or the frequency of the elevation in earlier years, the greater is the likelihood of high pressures later.

HEREDITY IN HYPERTENSION

A STATISTICAL STUDY

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CHARLOTTE, N. C.

From year to year the majority of those who discuss the causes of hypertensive cardiovascular disease list heredity as the chief, or at least a very important, factor.

This view is doubtless due to two clinical observations: In the first place, families in which a high percentage of the members in several generations have died from cardiovascular disease are frequently seen; but a generation ago the same was true of tuberculosis and led to the widespread idea that consumption was hereditary. In the second place, in the history of a majority of families, cardiovascular disease appears in each succeeding generation with noticeable frequency, owing, of course, to the high incidence of the disease in the general population. If the incidence of any hereditary trait is as high as 40 per cent, more than half the families in the general population will show the trait in both parents and children whether it be dominant or recessive. But this sort of evidence of heredity has the value merely of a "hunch."

O'Hare, Walker and Vickers [1] in Boston found a cardiovascular history twice as frequent among relatives of patients with hypertension as among relatives of controls, while Nuzum and Elliott [2] in California found the frequency of a cardiovascular history among relatives of patients with hypertension to be the same as among relatives of controls. Blanton [3] in Virginia found a family history of cardiovascular disease in 47 per cent of his patients with hypertension. As the ages and the relation of these relatives to the patients with hypertension and to the controls were not stated in any of these observations, such evidence is not competent. Weitz [4] obtained direct parental history of cardiovascular disease from 77 per cent of 82 patients with hypertension, and this evidence, so far as it goes, may be used to determine

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Read at the Forty-Eighth Annual Meeting of the Association of American Physicians, Washington, D. C., May 11, 1933.

1. O'Hare, J. P.; Walker, W. D., and Vickers, M. C.: Heredity in Hypertension, J. A. M. A. **83**:27 (July 5) 1924.

2. Nuzum, F. R., and Elliott, A. H.: An Analysis of 500 Cases of Arterial Hypertension, Am. J. M. Sc. **181**:630, 1931.

3. Blanton, W. B.: Study in Vascular Hypertension, South. Med. & Surg. **92**:495, 1930.

4. Weitz, W.: Etiology of Hypertension, Ztschr. f. klin. Med. **96**:151, 1923.

the inheritance of a unit trait, whether dominant or recessive. So far as I can find, this sums up the evidence for or against the heredity of hypertension.

For obvious reasons, in studying human heredity statistical methods must be used, and genetics, as based on Mendel's laws, being a mathematical science, definite percentages of parents, siblings and children of patients showing any unit trait will show the same trait. These percentages will depend on the incidence of the trait in the general population and on whether the trait is dominant or recessive. I have constructed tables [5] showing the expected incidence of any unit trait in parents, siblings and children of persons showing such trait, with incidences in the general population varying from 5 to 75 per cent. This gives something concrete to aim at, and in the study of any unit trait it remains for one to determine its incidence in the general population and to compare its frequency in parents, siblings and children with the percentages shown in the tables.

For the purpose of this study it is necessary to assume that hypertensive cardiovascular disease is inherited as a unit trait.

In considering hypertensive cardiovascular disease, the elevated blood pressure is merely the commonest and most easily measured symptom; so that only patients with hypertension have been used in this series. However, as clinical records of blood pressure date back only twenty years, other indications of hypertensive cardiovascular disease, such as apoplexy, sudden death from heart failure, and congestive heart failure, found in the histories have been given the same value as actual measurements of blood pressure in the patients.

A systolic pressure of 160 mm. of mercury or a diastolic pressure of 100 mm. has been used as the lower limit, indicating definite hypertension.

In trying to determine the frequency of hypertension in the general population, some fraction old enough to show the trait must be used. The actual finding of hypertension in persons more than 60 years of age should be the same as the potential presence of hypertension in those under 60, as modified by the following factors: First, some will have died of hypertension before the age of 60, but this positive evidence is not hard to get. Second, a few will have wasting diseases, such as cancer or tuberculosis, that obscure the trait. Third, some will not develop hypertension until after 60. Judging by clinical observation, the findings presented in this article are likely to be low rather than high.

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5. For construction of these tables see Allan, W.: The Inheritance of Migraine, Arch. Int. Med. **42**:590 (Oct.) 1928.

Such records of blood pressure as can be found at present in people over 60 years of age are derived chiefly from homes for the aged and from records of doctors and hospitals. These figures would naturally be somewhat too high. There are some figures obtained from insurance companies which, on the other hand, are likely to be somewhat too low. The New York Life Insurance Company, for instance, found that in 1931 heart diseases, apoplexy, nephritis and arterial diseases caused 32.5 per cent of the deaths of those insured by that company; in 1930, 47 per cent of the deaths of those above the age of 66 were due to these diseases. Table 1 shows the data easily available on the frequency of high blood pressure in persons more than 60 years old.

TABLE 1.—*High Blood Pressure in Patients More Than 60 Years Old*

Author	Age	Source	Blood Pressure	Number Examined	Number	Per Cent
Alvarez and Stanley: Arch. Int. Med. **46**: 17 (July) 1930	60+	Prisoners	160+	69	9	13
Willius: Am. J. M. Sc. **182**: 1, 1931	75-90	Mayo Clinic	160+	700	332	47
Davis: Human Biol. **2**: 264, 1930	75-83	Patients, J. H. H.	160+	50	21	42
Thompson and Todd: Lancet **2**: 503, 1922	75-92	Home for Aged, Eng.	160+	102	42	42
Allan: South. Med. & Surg. **92**: 491, 1930	61-95	Patients	160+	968	525	54
Wildt and Richter, quoted by Riseman and Weiss: Am. Heart J. **5**: 172, 1929	61-90	Patients	150+	409	183	45
Saller: Ztschr. f. d. ges. exper. Med. **58**: 683, 1928	60+	Outpatients	163+	510	194	38
Musser and Phillips, J. Lab. & Clin. Med. **15**: 633, 1930	70+	Outpatients	160+	50	21	42
Dublin, Fisk and Kopf: Am. J. M. Sc. **170**: 576, 1925	55+	Insured	152	1,094	252	23
				3,952	1,579	40

These figures indicate roughly that the incidence of hypertension in the general population is about 40 per cent.

My figures are based on findings in 485 patients with hypertension, 480 of whom gave direct parental history of hypertension, apoplexy, congestive heart failure or sudden death. This particular item is not a fair picture, since, in the absence of cardiovascular history, it is impossible to rule it out unless the parents live long enough and are actually examined.

Of the 480 patients one or both of whose parents had hypertension, there was a positive history for both parents in 131 instances, or 27 per cent, and for one parent in 349 instances, or 72 per cent. As may be seen in table 2, these figures are to be compared with expected frequencies of 32.4 per cent in both parents and 67.6 per cent in one parent in case the trait is dominant, and with 40 per cent in both parents

TABLE 2.—*Incidence of Unit Traits*

Incidence in General Population	Incidence of Any Unit Trait in Children When Present in: Both Parents D	Both Parents R	One Parent D	One Parent R	Neither Parent D	Neither Parent R	Incidence of Any Unit Trait When Present in Children in: One or Both Parents D	One or Both Parents R	Both Parents D	Both Parents R	One Parent D	One Parent R	Neither Parent D	Neither Parent R	Incidence of Any Unit Trait in Siblings of Those: With Trait D	With Trait R	Without Trait D	Without Trait R
5%	75.60	100	50.60	18.28	0	3.34	100	39.73	5.00	5	96.14	34.73	0	60.31	52.08	37.44	2.41	4.08
10%	76.28	100	51.30	24.00	0	5.76	100	53.25	7.62	10	92.34	43.25	0	46.76	54.36	43.34	5.07	6.30
15%	76.96	100	52.00	27.91	0	7.79	100	62.45	11.49	15	88.40	47.45	0	37.52	56.55	48.10	7.66	9.15
20%	77.70	100	52.78	30.90	0	9.55	100	69.45	15.51	20	83.86	49.45	0	30.56	58.29	52.36	10.27	11.91
25%	78.47	100	53.60	33.33	0	11.09	100	75.00	19.61	25	80.04	50.00	0	25.00	60.73	56.25	12.90	14.58
30%	79.24	100	54.45	35.40	0	12.53	100	79.55	23.77	30	76.23	49.55	0	20.45	63.45	59.89	15.67	17.19
35%	80.08	100	55.37	37.20	0	13.84	100	83.35	28.03	35	71.98	48.35	0	16.70	64.35	63.35	18.44	19.76
40%	80.97	100	56.37	38.75	0	15.01	100	86.50	32.39	40	67.65	46.50	0	13.51	68.15	66.61	21.25	22.25
45%	81.84	100	57.38	40.15	0	16.12	100	89.17	36.83	45	63.12	44.17	0	10.72	69.50	70.23	24.19	24.72
50%	82.84	100	58.58	41.42	0	17.15	100	91.42	41.42	50	58.58	41.42	0	8.58	72.86	72.85	27.14	27.14
55%	83.88	100	59.85	42.61	0	18.16	100	93.35	47.92	55	53.85	38.35	0	6.68	75.27	75.84	30.21	29.56
60%	84.99	100	61.25	43.62	0	19.03	100	94.90	51.00	60	49.00	34.90	0	5.00	77.80	78.72	33.38	31.88
65%	86.16	100	62.80	44.63	0	19.92	100	96.23	56.00	65	43.96	31.24	0	3.76	80.21	81.55	36.70	34.23
70%	87.47	100	64.60	45.55	0	20.75	100	97.33	61.15	70	38.76	27.33	0	2.68	82.80	84.33	40.12	36.56
75%	88.92	100	66.67	46.40	0	21.52	100	98.20	66.67	75	33.33	23.20	0	1.80	85.65	87.05	43.35	40.83
	79.6%		68.4%				99%		27%		72%		1%		60%			
Author's data	352+		469+				480+		131 both positive						501+			
	92—		216—				5—		349 one positive						333—			
	* 311 ?		500 ?				466 ?		5 both negative						843 ?			
	762		1,185				951		485						1,677			

and 46.5 per cent in one parent in case the trait is recessive. The early death of one parent in many instances would tend to increase the finding of hypertension in one parent instead of in both.

In 337 families in which the number of children was ascertained, there were 1,923 children, an average of 5.7 children or 4.7 siblings per family.

In 121 of the 337 families there was positive history of hypertension in both parents; of the 762 children in this group, 359 had hypertension, 92 did not, and 311 were too young or information concerning this fact was not obtained, giving a positive finding of 79.6 per cent. This is to be compared with 81 per cent in case of a dominant trait and 100 per cent in case of a recessive trait. In the other 216 families, there was a history of hypertension in one parent; of the 1,185 children in this group, 469 had hypertension, 216 did not, and 500 were too young or this information was not obtained, giving a positive finding of 68.4 per cent, as compared with an expected dominant frequency of 56 per cent and recessive frequency of 38.7 per cent. As yet, I have no control group of the children of normal persons large enough to tabulate.

In 349 families with 1,677 siblings of patients with hypertension, 501 had hypertension, 333 did not, and 843 were too young or this information was not obtained, giving a positive finding of 60 per cent in the siblings of these patients. As the expected frequency here is 68 per cent for a dominant trait and 66.6 per cent for a recessive trait, the study of siblings is not useful in differentiating between dominance and recessiveness, but tends to indicate the hereditary nature of hypertension. My data on the siblings of normal persons are not sufficient to tabulate.

The figures I have submitted suggest the possibility that hypertensive cardiovascular disease may prove to be a dominant unit trait, but they are much too few to warrant any definite conclusions. At the present time, therefore, the many statements in the literature that hypertension is either partly or wholly hereditary are without justification. This question can be answered only after many more facts have been gathered and analyzed from a genetic standpoint.

POLYTROPOUS ENTERONITIS (ACUTE INFECTIOUS GASTRO-ENTERITIS, SPENCER'S DISEASE)

IS IT A FORM OF INFLUENZA?

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Although influenza may be complicated by disturbances of the gastro-intestinal tract, many able clinicians have felt for some time that there is no true gastro-intestinal form of influenza in which the primary infection invades the alimentary canal. Boone [1] described a clinical condition with abdominal symptoms, which is usually called intestinal influenza, perhaps for want of a better name. Zahorsky,[2] McLean [3] and Lucas [4] described what is probably the same condition in children. Spencer [5] studied similar cases in the national parks of the West during the summers of 1929 and 1930. He stated that the disorder is a summer disease; on the other hand, Zahorsky said that the cases studied by him occurred in winter, and he accordingly gave the disease the name hyperemesis hiemis (winter vomiting disease).

The present report is based on a study of a group of about 750 college students seen between September, 1927, and June, 1932, who presented the same type of clinical picture, namely, sudden, acute onset of one or more of the following symptoms: nausea, vomiting, diarrhea, dull headache, abdominal distress. I believe that these cases and those described by Boone, Zahorsky, McLean, Lucas and Spencer are cases

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From the Department of Hygiene, College of Wooster.

The following assistance was given: statistical studies by Miss Miriam Winkler, my secretary; classification of isolated organisms by Dr. G. W. McCoy, Director of the National Institute of Health, Washington, D. C.; Dr. E. O. Jordan, Chairman of the Department of Bacteriology, the University of Chicago, and Dr. W. W. Ford, Professor of Bacteriology, Johns Hopkins University. Some epidemiological material was furnished by Dr. R. R. Spencer of the United States Public Health Service. Some of the drugs for the research were supplied by Sharp & Dohme, Baltimore, and by the William S. Merrel Company, Cincinnati.

1. Boone, F. H.: Gastro-Intestinal Grippe (So-Called), Canad. M. A. J. **19**:63, 1928.

2. Zahorsky, John: Hyperemesis Hiemis or Winter Vomiting Disease, Arch. Pediat. **46**:391, 1929.

3. McLean, C. C.: Seasonal Gastro-Enteritis, South. M. J. **24**:624, 1931.

4. Lucas, R. T.: Epidemic Vomiting or Intestinal Influenza, New Orleans M. & S. J. **83**:213, 1930.

5. Spencer, R. R.: Unusually Mild Recurring Epidemic Simulating Food Infection, Pub. Health Rep. **45**:2867, 1930.

of the same condition or very closely related conditions. The protean nature of this disorder, in which the symptoms are predominantly gastro-intestinal, makes fitting the proposed name "polytropous enteronitis" (polytropos-changeful, complicated; enteron-alimentary canal).[6] Because of Spencer's illuminating report and because he thought that the malady was a distinct disease, I shall also refer to it as Spencer's disease.

The findings here presented merely suggest an entity distinct from influenza, food poisoning and conditions with similar symptoms. Much more extensive investigation is needed to establish its identity firmly. Ordinary laboratory animals are not susceptible to the disorder. Human experimentation has been inexpedient. At the first opportunity I plan to use one of the simians. I have wondered if Jo Mendi, the trained chimpanzee at the Detroit zoo, was infected by human beings with polytropous enteronitis when he was so ill last year. The condition was called paradysentery.

ETIOLOGY

I have seen cases of polytropous enteronitis in persons ranging in age from 1 day to the late decades of life. My experience with the disease suggests that older children and young adults are more susceptible. Males and females are equally affected. I have known epidemics and sporadic cases of the disorder to occur at all times during the year. Personal observation in different localities, surveys and reports furnished by Dr. Spencer indicate that it is widely distributed and that climate has no influence. No predisposing factors have been determined. The responsible organism is unknown, but it is apparently spread by secretions from the nose and throat, as is illustrated by the following instance:

> L. B. was admitted to the hospital on May 22, 1930, because of nausea and a chilly feeling. The previous day she felt chilly and had malaise, a "light-headed" feeling and an intermittent headache. A diagnosis of polytropous enteronitis complicated by malaria was made. About 6 p. m. on May 23 she was visited by her brother, M. B., who took a sip of water from her drinking glass. At midnight on May 24 (thirty hours later) M. B. was suddenly seized with shifting abdominal cramps and diarrhea. The diagnosis was polytropous enteronitis. M. B. had been in the hospital under observation for a wholly unrelated condition since May 20. None of the hospital staff who ate the same food was ill. There were no other cases in the hospital and no contact with known cases other than that of L. B.

Atypical colon bacilli, atypical Flexner bacilli and atypical organisms belonging to the genus Salmonella were found in the stools of the

6. Suggested by Miss Eva May Newman, Assistant Professor of Greek, College of Wooster.

patients whom I was treating for this condition. McBroom [7] found atypical organisms of this group in a series of patients with various gastro-intestinal disorders. Therefore the presence of such organisms may be a coincidence. Fothergill [8] found slow lactose-fermenting gram-negative bacilli in the stools of infants with diarrhea. Some research workers have suspected such organisms of being more virulent than the ordinary organisms of the colon group. Most of the atypical organisms found presented some characteristics resembling the colon bacillus, even the atypical Flexner bacilli. Since I could produce no agglutinating serums with vaccines sterilized by heat or formaldehyde or with young living cultures, I was unable to determine the relationships serologically.

Cultures of any organisms taken from the throats of patients, when fed to mice, produced slowing of lactose fermentation by colon bacilli taken from their rectums. Attempts to isolate a symbiotic filtrable virus capable of producing such a change in colon bacilli were unsuccessful. Electrophoretic studies [9] of these organisms were not carried far enough to yield any suggestive data. As matters stand, I do not know whether these organisms are present as the cause or as the result of the disease, or whether they are merely coincidental. They could not be isolated from cultures taken from the throats of patients.

Attempts to isolate the organisms described by Rockwell,[10] Rosenow,[11] Fellman,[12] Harrington [13] and Hinkelmann [14] were unsuccessful. I believe that, with the exception of Rockwell, these investigators were dealing with a clinical entity other than polytropous enteronitis, in view of the fact that the conditions which they described were more serious and more persistent and were at times fatal. None of the patients in the group studied by me died or appeared to be dangerously ill.

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7. McBroom, Josephine: Paratyphoid, Proteus and Related Organisms in Health and in Miscellaneous Intestinal Disorders of Man, J. Prev. Med. **4**:239, 1930.

8. Fothergill, L. D.: Unusual Types of Non-Lactose Fermenting Gram-Negative Bacilli from Acute Diarrhea of Infants, J. Infect. Dis. **45**:393, 1929.

9. Lieb, C. W., and Chapman, G. H.: Studies in Intestinal Intoxication, New York State J. Med. **29**:1323, 1929.

10. Rockwell, G. E.: Report of Five Cases of Intestinal Grippe, with Bacteriologic Findings, J. Med. **8**:82, 1927.

11. Rosenow, E. C.: Experiments in Etiology of Gastro-Intestinal Influenza, J. Infect. Dis. **26**:557, 1920.

12. Fellman, G. H.: Report of Epidemic of Gastro-Enteritis, Wisconsin M. J. **20**:227, 1921.

13. Harrington, A. H.: Acute Infectious Enteritis with Polyneuritic Symptoms, Bull. State Board of Health of Rhode Island **3**:17, 1917.

14. Hinkelmann, A. G.: Bacteriology of So-Called Gastro-Intestinal Influenza, Illinois M. J. **28**:353, 1915.

Although I have been successful in isolating pleomorphic organisms from the blood and saliva of patients with influenza by using Kendall's [15] technic, cultures made from filtrates of the stool and saliva and cultures made from the blood of patients with polytropous enteronitis were sterile. If the organisms described by Kendall and by Olitsky and Gates [16] are the cause of influenza, it seems that one should be able to find them as frequently in patients with polytropous enteronitis as in those with influenza, if the two conditions are forms of the same disease.

In an epidemic among the students of the College of Wooster in November, 1927, Bacillus pyocyaneus was isolated in large numbers from the milk used in the women's dining rooms. The explosive nature of the epidemic suggested food poisoning, but the organisms in the milk were all that could be found that was suggestive of the source of trouble. Epidemiologically and clinically, the outbreak was wholly unlike the one described by Cooley.[17] The fact that I was dealing with college students instead of infants may account for some of the differences noted. There is a question whether the epidemic was caused by poisoning with the products of B. pyocyaneus or by polytropous enteronitis. B. pyocyaneus has not been found in the milk since that time. A colony of atypical proteus bacilli [18] was found in a culture from one sample of milk, and on another occasion an organism resembling a staphylococcus [19] was found, which failed to grow on subcultures from the original blood agar plates.

The feeding of isolated atypical organisms failed to produce symptoms in rats and mice. Atypical Flexner bacilli affected the animals only when given intraperitoneally. When they were so given in small doses the animal showed few if any signs of illness and rapidly destroyed the organisms. Serial passage through animals failed to

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15. Kendall, A. I.: A Filterable Organism from Influenza, Science **74**:129, 1931.

16. Olitsky, P. K., and Gates, F. L.: Experimental Studies of Nasopharyngeal Secretions from Influenza Patients, J. A. M. A. **74**:1497 (May 29) 1920.

17. Cooley, T. B.: An Epidemic of Infantile Diarrhea Apparently Caused by Bacillus Pyocyaneus, J. A. M. A. **50**:607 (Feb. 22) 1908.

18. Bengston, I. A.: Proteus Group of Organisms with Special Reference to Reactions of Agglutination and Fermentation and Classification, J. Infect. Dis. **24**: 428, 1919.

19. (*a*) Jordan, E. O.: Production by Staphylococci of Substances Causing Food Poisoning, J. A. M. A. **94**:1648 (May 24) 1930; Staphylococcus Food Poisoning, ibid. **97**:1704 (Dec. 5) 1931. (*b*) Jordan, E. O., and Hall, J. B.: Case of Food Poisoning Apparently Due to Staphylococcus, J. Prev. Med. **5**:387, 1931. (*c*) Dack, G. M.; Cary, W. E.; Woolpert, O., and Wiggers, H.: Outbreak of Food Poisoning Proved to Be Due to Yellow Hemolytic Staphylococcus, ibid. **4**: 167, 1930.

increase the virulence of the organisms. When sufficient doses were given the animals usually died within about twelve hours, apparently from toxemia.

EPIDEMIOLOGY

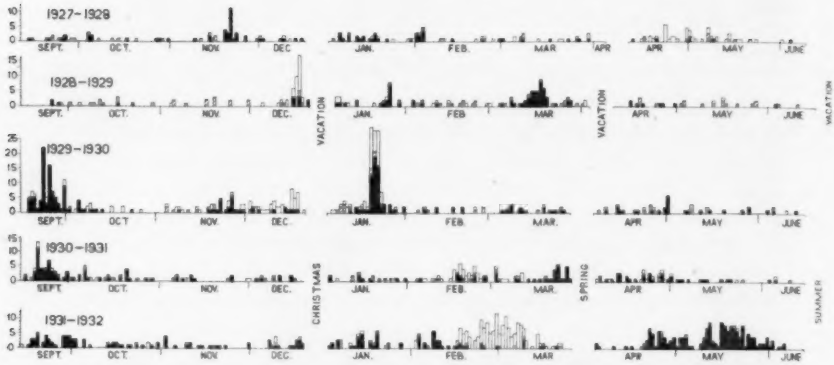
As I have indicated, the relation of Spencer's disease to influenza is doubtful, but epidemics of a condition like Spencer's disease have been reported in close association with epidemics of influenza since the World War. This is probably a coincidence. As is shown by the accompanying chart, only once in five years did epidemics of the two disorders occur simultaneously in the group studied (January, 1930). I noticed a marked increase in the number and virulence of cases a few weeks after the marked epidemic of influenza in February and March, 1932.

Although differential diagnosis is difficult at times, the two disorders are as a rule clinically different. Table 1 shows that polytropous enteronitis and influenza do not confer immunity against one another. It will also be noted that influenza confers immunity lasting at least two months to subsequent attacks of the same disorder. Vaughan and Jordan (quoted by Rosenau [20a]) believed that immunity in influenza probably does not last more than seven months. In polytropous enteronitis, however, the immunity is apparently of much shorter duration than in influenza, as is indicated in table 1. Recurrent attacks occur at intervals of from one to six weeks. One patient reported eleven successive attacks in about as many weeks. Fortunately, this is unusual.

Food and water are apparently not vectors, although they may be transient fomites. The condition is not food poisoning. The organisms of typical food poisoning were absent in patients and in suspected food. There were no common food factors. The sources of food, milk and water varied widely. Laboratory animals which are ordinarily susceptible to food poisoning could not be infected with the infective material taken from patients. Cases developed within from twenty-four to forty-eight hours following contact with a known case, and epidemics usually reached their peak within from three to five days instead of from one and one-half to twelve hours after the eating of a suspected meal, as would be the case with food poisoning. The incubation period in food poisoning may be as long as thirty hours, but the epidemic peak is reached within a few hours.

The city and campus water supplies are independent, and some students commuting daily from surrounding rural areas rarely, if ever,

20. Rosenau, M. J.: (*a*) Preventive Medicine and Hygiene, ed. 5, New York, D. Appleton and Company, 1927, p. 245; (*b*) Some Fallacies in Diagnosis of "Ptomain Poisoning," M. Clin. North America **2**:1541 (March) 1919; (*c*) Experimental Lunch with Canned Food Containing Bacteria, ibid. **3**:913 (Jan.) 1920.



Relation of polytropous enteronitis to influenza, as shown by the incidence of cases. The black columns indicate polytropous enteronitis; the white columns, influenza, and the white columns with diagonal lines, undiagnosed condition with symptoms similar to those of polytropous enteronitis.

TABLE 1.—*Immunity Reactions in Polytropous Enteronitis and in Influenza* *

Polytropous Enteronitis		Influenza		Polytropous Enteronitis and Influenza	
Case	Date of Attack	Case	Date of Attack	Case	Date of Attack
20 E.....	3/11/29	86 B.....	(10/ 4/28)	181 F.....	1/20/32
	3/18/29		(12/15/28)		(2/26/32)
128 F.....	1/ 4/32				5/12/32
	1/20/32	245 D.....	(3/29/28)	19 B.....	4/12/28
291 G.....	11/ 8/30		(2/15/31)		(4/15/28)
	3/25/31		(4/27/31)	291 G.....	2/25/32
	1/28/32				(2/29/32)
	2/25/32	121 H.....	(12/17/31)		3/ 7/32
	3/ 7/32		(3/ 7/32)	143 B.....	1/18/29
	5/14/32				(1/21/29)
	5/27/32†	212 D.....	(2/23/28)	71 F.....	1/ 7/32
	6/ 6/32		(5/ 7/28)		(2/11/32)
23 H.....	3/27/32				5/25/32
	4/ 3/32	213 H.....	(2/27/32)	96 C.....	(12/18/28)
44 G.....	2/27/31		(4/26/32)		1/15/29
	3/17/31			131 F.....	2/11/30
	3/27/31				(2/17/30)
43 D.....	11/21/29			124 G.....	(2/24/31)
	12/14/29				3/22/31
	1/21/30				
	9/22/30				
	2/20/31				
	3/23/31				

* Cases of influenza are enclosed in parentheses; other cases are those of polytropous enteronitis. It should be noted that recurrent attacks of polytropous enteronitis occurred at intervals of a week or more, whereas no two attacks of influenza were less than eight weeks apart. Furthermore, attacks of typical influenza followed attacks of polytropous enteronitis in as short a time as three days. Patient 291 G had typical polytropous enteronitis four days following the onset of mild respiratory influenza from which she was convalescing when the attack occurred.

† Reported eleven recurrent attacks since Feb. 1, 1932.

drink water on the campus. The campus water comes from deep wells and shows only an occasional air contaminator on bacteriologic examination. The city water, which comes from a 40 foot (12 meter) well in a valley, is examined on the average every two weeks; it has shown Bacillus coli only twice in six years and then only when there were bad floods. The milk is of exceptional quality from a bacteriologic standpoint.

Animals are apparently not vectors. The college kitchens are kept unusually free from rodents and flies. A third of the students or less board off the campus.

Since I had patients in whom the mode and time of contact with other cases were known with certainty, I feel amply justified in drawing the conclusion that the infection is spread by secretions from the nose and throat. The epidemiologic characteristics point to the same source of infection. Room-mates may transmit the disease to one another, and in the dining halls several students at one table may have the condition, while those at other tables may be free. I have not been able to settle the question of healthy carriers.

PATHOGENESIS

Although the organisms seem to be in the nose and throat, only about 10 per cent of the patients complained of respiratory symptoms. Aching and tenderness over the frontal sinuses suggested irritation and toxic absorption from their mucous membranes, but the clearness revealed by transillumination and the appearance of the visible parts of the respiratory mucous membranes indicated that there was little congestion except in patients with definite respiratory symptoms. The infrequency of leukocytes in the stools suggested that a similar condition obtained in the alimentary canal, a point which might be partly settled by gastroscopy and sigmoidoscopy.

Unfortunately, vomitus was not carefully examined. There were no red cells in the stools, but I did not make tests for occult blood which might account for the darker stools in some cases. In one epidemic a patient with atypical acute appendicitis had a large, swollen, spindle-shaped appendix, with three large hemorrhagic areas under the serosa. Phillip Potter [21] of Bellevue Hospital noted in a patient with a similar condition petechial hemorrhages under the serosa of the terminal part of the ileum and under that of the cecum and appendix, with red lymph nodes in the region. St. John [21] of the New York Presbyterian Hospital noted cherry red abdominal lymph nodes in another patient. In the typhlo-appendical type of Spencer's disease there is usually tenderness over the region of the terminal part of the ileum and over the

21. Personal communication.

cecum and appendix. A child, aged 6, whom I saw in Detroit in May, 1926, had abdominal lymphadenitis; a normal appendix was removed at operation. This may have been a case of the typhlo-appendical type of Spencer's disease. F. F. Russell, director of the International Board of Health, told me of the finding of exudative peritonitis in a patient on whom an operation was performed during an epidemic in the Canal Zone. Two other patients with similar conditions recovered without an operation. Whether secondary invaders play a part in the production of such pathologic conditions I cannot say. Some of the atypical organisms found in the stools were hemolytic.

Fairbanks [22] discussed the neurologic aspects of food poisoning. In polytropous enteronitis there is much evidence of imbalance of the autonomic nervous system, with the effect of the vagus predominating. Peripheral neuritis is common, and there may be myositis, particularly of the abdominal wall. There is tenderness over portions of the spine, particularly over the three upper dorsal vertebrae. These rheumatoid symptoms suggest a toxic or metastatic disorder. Whether it is due to the primary infection or to the secondary invaders is not clear. Vasomotor instability, largely in the abdominal viscera, may result partly from autonomic imbalance and partly from local toxic vasodilatation.

The fact that a considerable number of patients have recurrent attacks after a six day interval suggests that the disease may have a phasic nature. One woman student reported eleven recurrent attacks in about as many weeks, causing me to wonder if the condition might be an allergic phenomenon. One attack occurred on the second day after the fever had gone down following an attack of mild respiratory influenza. I could not account for the attacks on the basis of any other gastro-intestinal condition than Spencer's disease. Only one patient, a woman with a chronic disorder of the bowels which was diagnosed as irritable colon, was tested for allergic phenomena according to the method of Dorst and Morris.[23] She was apparently sensitive to Bacillus cloacae taken from the stool during an attack of polytropous enteronitis, but the preparation of vaccine for the test could not be completed until several days after the attack had subsided. The chronic condition was apparently temporarily improved after the reaction to the sensitization test had subsided.

SYMPTOMS

Clinically, polytropous enteronitis, or Spencer's disease, is characterized by an acute, sudden onset of one or more of the following symp-

22. Fairbanks, A. W.: Neurologic Aspects of Food Poisoning, Boston M. & S. J. **176**:413, 1917.

23. Dorst, S. E., and Morris, R. S.: Bacterial Hypersensitivity of Intestinal Tract, Am. J. M. Sc. **180**:650, 1930.

toms named in the approximate order of their frequency: anorexia or nausea, vomiting, diarrhea, dizziness on standing, dull headache which is usually frontal, aching in the back and legs or generalized aching, abdominal distress or cramps, chiliness or alternate sensations of heat and cold, cold in the head, sore throat, constipation. Retching is rare; tenesmus is unusual, and blood has never been noted in the stools grossly or microscopically. Vomiting may be almost projectile at times. The usual incubation period is from thirty to thirty-six hours.

PHYSICAL FINDINGS

Physical examination frequently shows nothing significant. The patient may not appear markedly ill unless he is vomiting, although children may have an ashy look, sunken eyes, a listless expression and an acetone breath. The skin is usually dry or flushed; it is rarely cool and moist, with some pallor, and in children it is dehydrated. Red dermographia is present. The temperature is frequently subnormal; fever is slight and transient as a rule, but may rise to 104 F. in severe cases; a relatively slower pulse at the febrile fastigium is common.

There is usually tenderness over portions of the colon, especially over the sigmoid flexure. Sometimes there is tenderness over McBurney's point and the epigastrium. The abdominal wall may be tender, particularly over the rectus abdominis muscles. The spleen appeared to be transiently enlarged in one patient, a boy 5 years old. There may be tenderness over some of the vertebrae, especially over the first three dorsal segments, and also along the trunks of the spinal nerves and their areas of distribution.

When there are respiratory symptoms, the nose and throat may exhibit a slight redness or injection, sometimes swelling, and rarely discharge. These symptoms and findings may be a coincidence, but they precede the development of other symptoms by an interval of about two days so often as to suggest a definite relationship to the disease in some cases. In spite of tenderness over the frontal sinuses, the latter are as clear to transillumination as usual. There are marked dizziness and a sudden rise and fall of blood pressure on standing, resulting in a fall of pulse pressure.

LABORATORY FINDINGS

The blood may show polymorphonuclear leukocytosis, with as many as 15,000 cells per cubic millimeter, which is often followed by secondary leukopenia about twenty hours later (table 2). The stools are frequently offensive in odor; they are sometimes darker than normal, and, in early diarrhea, are watery, with fine flecks of mucus but with no pus or blood cells. Undigested particles of food are rarely present. Mucus

is abundant later. Atypical organisms of the colon group apparently persist for about from ten days to two weeks after the attack.

COURSE AND TYPES

Acute symptoms often last only from eighteen to twenty-four hours and are followed by rapid recovery from the residual weakness. Diarrhea may last two weeks in some epidemics; in some cases it may last as long as three weeks. Dizziness on standing lasted as long as six weeks in one patient and four weeks in another.

For convenience of study I have divided cases of this disorder into six types, listed in the relative order of their frequency, with their predominant symptoms:

Type 1. Gastro-enteric: nausea, vomiting, diarrhea

Type 2. Enterocolic: diarrhea, sometimes cramps

Type 3. Gastric: anorexia, nausea, vomiting

Type 4. Neurocirculatory: dizziness, dull headache

Type 5. Typhlo-appendical: like acute appendicitis except for diarrhea, dizziness on standing and dull headache; fever less constant; less marked and less sharply localized tenderness in lower part of right quadrant; less rigidity of abdominal wall

Type 6: Colic: Cramps or severe midabdominal pain, usually with constipation

COMPLICATIONS AND PROGNOSIS

Unless respiratory symptoms are considered as complications, the latter were rare in my series. In two or three instances subacute exacerbation of chronic appendicitis apparently complicated a case of the typhlo-appendical type of Spencer's disease. A flare-up in a malarial infection, caused by polytropous enteronitis, made differential diagnosis difficult in one case.

Although a large number of the patients were very ill, there were no deaths due to this condition and, so far as I know, no sequelae. I have known about a third of the student body of the college to be ill during an epidemic, most of them within one week. From three to five distinct epidemics occurred each year, and large numbers of sporadic cases occurred throughout the year. The morbidity rate was amazing; some patients remained in bed and were severely ill for three or four days at a time, and many others were partially incapacitated for as long as two weeks or longer.

DIFFERENTIAL DIAGNOSIS

There is a great variety of conditions which must be differentiated from polytropous enteronitis. Some of these, in which differentiation is extremely important, will be mentioned. Vigilance in regard to food

poisoning [24] must never relax. So far as I know, no one has ever died from Spencer's disease, but food poisoning has a significant mortality rate. Therefore, one must promptly detect and remove the source of food poisoning as well as find and treat efficiently all persons suspected of having it. The same statements apply to typhoid and to bacillary [25] and amebic dysentery, which may at times be difficult to differentiate. Some fishes and mushrooms, potatoes grown or stored under certain conditions,[22] the leafy portions of rhubarb, saltpeter used for the preservation of meat [20b] and foods contaminated by staphylococci,[19] streptococci,[26] B. enteritidis,[27] B. paratyphosus A and B,[28] B. suipestifer (aertrycke) [29] and, possibly, B. proteus,[30] B. cloacae,[31] B. coli and B. subtilis [22] may be responsible for a clinical picture which can be differentiated from polytropous enteronitis only with difficulty. Botulism [32] is so distinctive that it offers no difficulty in regard to diagnosis, unless it is complicated by other types of food poisoning or by other conditions.

Water containing increased amounts of organic matter has been blamed for epidemics similar to those of polytropous enteronitis in some cities of the Ohio River valley.[33] I doubt that commercial canned goods ever produce food poisoning, unless they are obviously spoiled.[20c]

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24. (*a*) Jordan, E. O.: Food Poisoning and Food-Borne Infection, ed. 2, Chicago, University of Chicago Press, 1930. (*b*) Geiger, J. C.: Poisoning by Food Probably Due to Contamination with Certain Bacteria; Epidemiologic Analysis of Seven Hundred and Forty-Nine Reported Outbreaks in the United States, J. A. M. A. **81**:1275 (Oct. 13) 1923. (*c*) Rosenau, M. J., and Weiss, Harry: Food Infections with an Illustrative Outbreak, J. A. M. A. **77**:1948 (Dec. 17) 1921.

25. Warren, S. H.: Outbreak of Illness Caused by B. Dysenteriae Flexner, Lancet **2**:494, 1927.

26. Cary, W. E.; Dack, G. M., and Myers, E.: Institutional Outbreak of Food Poisoning Possibly Due to Streptococcus, Proc. Soc. Exper. Biol. & Med. **29**:214, 1931.

27. Fairbanks.[22] Rosenau and Weiss.[24c]

28. Bernstein, H. S., and Fish, E. S.: Food Poisoning by the Bacillus Paratyphosus B, J. A. M. A. **66**:167 (Jan. 15) 1916. Geiger, J. C., and Jordan, E. O.: Two Outbreaks of Food Poisoning Apparently Due to Bacilli of Paratyphoid Enteritidis Group, J. Infect. Dis. **32**:471, 1923. Fairbanks.[22] Rosenau and Weiss.[24c]

29. Gill, D.: Fatal Food Poisoning Due to Bacillus Suipestifer, Brit. M. J. **2**: 857, 1924. McWeeney, E. J.: Gastro-Enteritis Due to Bacillus Aertrycke, Brit. M. J. **2**:451, 1916.

30. Bengston.[18] Fairbanks.[22] Jordan,[24a] p. 141.

31. Buchanan, E. B., and Megrail, E.: Two Outbreaks of Food Poisoning Probably Due to B. Cloacae, J. Infect. Dis. **44**:235, 1929.

32. Burke, Victor, and May, C. W.: Presumptive Test for Etiologic Factor in Bacterial Food Poisoning, J. A. M. A. **79**:1669 (Nov. 11) 1922. Fairbanks.[22]

33. Veldee, M. V.: An Epidemiologic Study of Suspected Water-Borne Gastro-Enteritis, Am. J. Pub. Health **21**:1227, 1931.

The typhlo-appendical type of polytropous enteronitis may simulate acute appendicitis closely or may even stir up an old chronic appendical infection. If there is doubt, it is better to remove a normal appendix than to risk a fatal issue from pyogenic appendicitis. I have had several patients with subacute exacerbation of chronic appendicitis which subsided without operative intervention within one or two weeks after a flare-up caused by polytropous enteronitis.

The colic type frequently resembles other acute abdominal conditions. In this type codeine and enemas are used freely, but they may lead to disastrous results in mesenteric thrombosis, volvulus, intussusception or strangulation of the bowel. A "lightheaded" or dizzy feeling on standing and dull aching over the frontal sinuses are two of the most characteristic symptoms of polytropous enteronitis, but they should not be accepted as absolutely pathognomonic.

Error in diagnosing some conditions, e. g., catarrhal jaundice and influenza with gastro-intestinal symptoms, is not serious, but may delay recovery through lack of proper treatment. In catarrhal jaundice, abdominal distress is high (epigastric), and there is often tenderness over the liver. Light-colored stools, bloating, eructations and malaise are the rule even before the jaundice is evident. Transduodenal stimulation with a 25 per cent solution of magnesium sulphate, hot olive oil and hot saline drip are in order, measures which are entirely out of place in Spencer's disease. In influenza the abdominal symptoms usually appear later than in Spencer's disease; the weakness and depression are more marked, and the leukopenia is primary instead of secondary, with leukocytosis occurring later in some instances. Convalescence is slower, and the patient requires more prolonged nursing to avoid complications and sequelae.

Burgess [34] described influenza complicated by jaundice. The appearance of gastro-intestinal symptoms at a later time than in Spencer's disease is noteworthy. Abels [35] also described cases in which there were gastro-intestinal symptoms. The early appearance of gastro-intestinal symptoms in a case described by Blake [36] raises a question as to the accuracy of the diagnosis of influenza. Leukopenia was noted several days after the onset, which would be consistent with polytropous enteronitis.

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34. Burgess, A. M.: Influenzal Gastro-Duodenitis with Jaundice, Rhode Island M. J. **6**:166, 1923.

35. Abels, H.: Das selbständige Magen-Darmbild der Grippe, Wien. klin. Wchnschr. **41**:1482, 1928.

36. Blake, G.: "Intestinal Influenza," M. Clin. North America **8**:1545 (March) 1925.

Migraine, gastric crises and many other conditions in which gastrointestinal symptoms occur must also be kept in mind in making the differential diagnosis.

REPORT OF CASES

Gastro-Enteric Type.—A girl, aged 19, on Dec. 10, 1931, felt tired and complained of aching back of the eyes and in the temples; her throat was "rough"; she had had a nasal discharge for a week. She could not sleep because of epigastric heaviness and fulness. About midnight there was nausea, with a dull epigastric ache. She vomited at 4 a. m. and felt dizzy and faint on rising. That morning there were stiffness and a tired feeling between the shoulders; the legs were tired; she vomited several times. She passed a slightly constipated stool at 8:30 a. m. and took a cathartic at noon. She was admitted to the hospital at 1 p. m. with a temperature of 98.6 F. and a pulse rate of 108. She appeared somewhat ill; the skin was warm and dry; the nose was slightly red and moist. The sinuses were clear, and examination of the throat showed nothing significant; the posterior cervical lymph nodes were slightly enlarged but were not tender. Examination of the abdomen gave negative findings. There was slight tenderness over the following vertebrae: the first cervical, the first four dorsal and the fourth and fifth lumbar. Atropine sulphate in a dose of 0.0012 Gm. was given intramuscularly at 3:15 p. m. The temperature was 100 F. and the pulse rate was 112 at 4 p. m. The white blood count at 3:30 p. m. was 14,500 per cubic millimeter, with 88 per cent polymorphonuclears, 8 per cent small mononuclears and 4 per cent large mononuclears. She passed a loose stool at 3:15 p. m. At 8 p. m. the temperature was 101 F. and the pulse rate was 92. She experienced slight nausea two or three times after the administration of the atropine. She tolerated water well. During the evening there was considerable headache, which was relieved by 1 Gm. of acetylsalicylic acid given at 9 p. m. The next morning the patient's condition was normal except for weakness. She passed a loose stool at 10 a. m. The white blood count was 4,500 at 10 a. m., with 85 per cent polymorphonuclears, 12 per cent small mononuclears, and 3 per cent large mononuclears. The temperature was 97.4 F. and the pulse rate was 72 at 8 a. m. Camphorated tincture of opium in a dose of 4 cc. was given at 6:10 p. m. for diarrhea. She passed a stool at 10 p. m. All the symptoms were gone the next morning, and the patient was discharged.

Enterocolic Type.—A youth, aged 21, on the morning of April 18, 1932, had a "cold in the head," which was worse the next day but improved on April 20. About 4 a. m. on April 21 he had cramps in the upper part of the abdomen and thought that he would have felt better if he could have belched. At 6 a. m. he passed a soft stool, and at 10 a. m. he passed a loose stool without tenesmus, blood or visible mucus. The stool was darker than normal. During the morning there were malaise and a dull frontal headache. I saw him at 11 a. m. because of severe cramplike pain in the upper part of the abdomen. He looked quite ill. The mucous membrane of the nose was slightly swollen, and there was a mucous discharge. There may have been a slight swelling of lymphoid tissue of the throat. The anterior and right posterior cervical lymph nodes were swollen but were not tender. The sinuses were not tender, but the right maxillary sinus was hazy. The temperature was 98.4 F., and the pulse rate was 88. The systolic and diastolic blood pressures were 92 and 66 respectively when the patient was in a recumbent position (they had been 104 and 72 on Oct. 1, 1931). The white blood count was 11,300. A differential count showed 89 per cent poly-

morphonuclears, 6 per cent small mononuclears, 2 per cent large mononuclears, 2 per cent transitionals and 1 per cent basophils. The oculocardiac reflex showed a slowing of the pulse rate from 88 to 72. The blood pressure when the patient was standing was 101 systolic and 81 diastolic. There was no dizziness. Atropine in a dose of 0.0012 Gm., given at 11:15 a. m., relieved the pain, and the patient left the office at 3 p. m. The next morning he reported that he had passed loose stools twice during the afternoon and evening and again at 7:20 a. m. He experienced slight pain in the upper part of the abdomen after meals. Weakness was the only other symptom. The white blood count was 5,750 at 11:30 a. m. The differential count was unsatisfactory.

Gastric Type.—A girl, aged 17, had a dull frontal headache and an aching through the eyes at 4 p. m. on Dec. 12, 1931. She vomited four or five times during the night; there was a dull generalized headache; she felt very dizzy on rising. There was slight abdominal soreness with heaviness after meals. A normal stool was passed on December 13. She was admitted to the hospital at 11 a. m. on December 14, with a temperature of 97 F. and a pulse rate of 80. Sodium nitrite in a dose of 0.12 Gm. produced no change in the dizziness. One cubic centimeter of epinephrine given intramuscularly at 4:30 p. m. improved this symptom. One cubic centimeter of a 3 per cent solution of ephedrine sulphate was given orally. This was followed by some nervousness and palpitation. The patient received 0.06 Gm. of phenobarbital at 9:30 p. m. Tincture of belladonna relieved the epigastric soreness and heaviness which began a half hour after supper. The temperature was 98.6 F. and the pulse rate was 88 at 8 p. m. The patient passed a hard stool that night. The next morning there was burning in the epigastrium after breakfast. On December 16 dizziness was the only symptom; this lasted ten days. There was no fever. The patient was discharged at 10 a. m. on December 17.

Neurocirculatory Type.—A girl, aged 19, had a dull frontal headache, shifting pain in the lower part of the abdomen, nausea and slight vertigo on the afternoon of April 22, 1932. After passing a constipated stool she felt better, and the next day her condition was normal. At noon on April 25 the frontal headache returned and was worse than before. There were dizziness and a chilly feeling. There was no stool from April 22 until she was seen on April 25 at 5:30 p. m. The white blood count was 11,650. A differential count showed: polymorphonuclears, 70 per cent; small mononuclears, 21 per cent; large mononuclears, 4 per cent; transitionals, 1 per cent; basophils, 5 per cent. The systolic and diastolic blood pressures were 106 and 74 respectively when the patient was in a recumbent position, and the pulse rate was 80. When the patient was standing the immediate blood pressure was 138 systolic and 92 diastolic and the pulse rate was 76; after one minute the blood pressure was 104 systolic and 82 diastolic. Epinephrine increased the dizziness. Atropine in a dose of 0.0012 Gm. was given at 5:34 p. m. The patient was dizzy most of the evening but slept well. The headache was gone the next morning. Except for a slight weakness she felt well, and was discharged at 9 a. m. The maximum temperature was 98 F.

Typhlo-Appendical Type.—A girl, aged 20, felt dizzy, chilly and weak and had aching and sharp pain in the middle part of the abdomen at 9 a. m. on April 26, 1932. There had been a normal stool the night before. She was admitted to the hospital at 7 p. m. with a temperature of 100 F. and a pulse rate of 118. The cervical lymph nodes were unaffected; the sinuses were clear and were not tender. The mucous membrane of the nose was slightly red on the left side. The throat did not relax well. Abdominal examination showed a slight tenderness over the cecum, the terminal part of the ileum, McBurney's point and the transverse,

descending and sigmoid colon. Treatment with heptylresorcinol, a salt water enema and a heat pad was instituted. The temperature was 102 F. at 8 p. m. on April 27 and was within normal range on the morning of April 29. On April 27 examination of the abdomen gave negative findings; the only symptom was slight abdominal soreness on movement. On April 28 the patient felt well in spite of fever; the face was flushed. On April 29 she felt even better; the flush was gone. She was discharged at 6:30 p. m.

Colic Type.—A youth, aged 20, had a "stomach ache" while walking up the hill from town at 11:30 p. m. on Feb. 24, 1933. He took sodium bicarbonate and a cathartic during the night because he thought that he might feel better if the bowels would move. He came to the hospital at 7:30 a. m. on February 25. The temperature was 99.4 F., and the pulse rate was 78. A heat pad failed to give relief. At 9 a. m. a hypodermic injection of 0.0012 Gm. of atropine sulphate and 0.06 Gm. of codeine was given. This gave little relief. The severe aching pain

TABLE 2.—*Leukocytosis and Leukopenia in Polytropous Enteronitis*

Leukocytosis		Leukopenia		Leukocytosis Followed by Leukopenia	
White Blood Cells per Cu.Mm.	Time After Onset	White Blood Cells per Cu.Mm.	Time After Onset	White Blood Cells per Cu.Mm.	Time After Onset
13,000	2¾ hrs.	3,200	A few hours?	{11,300	{ 7 hrs.
9,500	11 hrs.	6,600	Same day	{ 5,750	{31 hrs.
11,500	12 hrs.*	3,500	12 hrs.	{13,700	{Same day
8,300	12 hrs.*	5,900	21 hrs.?	{ 5,800	{14 hrs. later
8,500	17½ hrs.	4,600	21 hrs.		
9,300	21 hrs.?	4,100	32 hrs.		
8,650	24 hrs.*	3,900	2 days		
12,150	3 days	6,000	2 days		
8,300	4 days				

* Approximately.

was well localized just above the umbilicus. There was tenderness over the rectus abdominis muscles, particularly just above the umbilicus. The patient said that the heat seemed to aggravate the distress, so the heat pad was removed. The pain was worse when the patient sat or stood. He slept the latter part of the morning; at noon a hot salt water enema was given. There was some dysuria when the bowels moved after the enema. The patient seemed to be more comfortable in the afternoon and slept for some time. The temperature and pulse rate were 99.8 F. and 88 respectively at 3 p. m.; at 8 p. m. they were 99.8 F. and 68, and at 9 p. m. they were 99 F. and 68. At 1:15 a. m. on February 26 the pain was worse. Another hypodermic injection of atropine and codeine gave some relief. That day the patient was fairly comfortable except for weakness and abdominal soreness on rising. The temperatue ranged from 97 F. to 98.6 F., and the pulse rate ranged from 60 to 66. One and three-tenths cubic centimeters of tincture of belladonna was given three times a day before meals. On February 27 the patient was better and was discharged with instructions to continue taking the belladonna until the distress was gone. On March 4 he reported that he had not noticed any definite abdominal soreness for two or three days but that there was still some weakness. He said that he feared a recurrence of the pain and was continuing to take 1.3 cc. of tincture of belladonna before meals.

Cases of obscure dull headache, dizziness and nervousness, malaise, anorexia, vague abdominal distress and obscure gastro-intestinal complaints frequently occurred in close association with epidemics and sporadic cases of typical polytropous enteronitis. Many of them were abortive cases of this disease. They are not described here because they were not typical enough and because their relationship was not sufficiently clear to justify their inclusion in the present report. When obscure complaints of this type present themselves, polytropous enteronitis should be kept in mind in making the differential diagnosis.

TREATMENT

In the general treatment prompt, thorough evacuation of the gastro-intestinal tract, with abstinence from food for twenty-four hours is indicated. Drastic cathartics are contraindicated. Magnesium sulphate taken by patients on their own initiative definitely aggravated the intestinal symptoms. Magnesium oxide, magnesia magma, cascara sagrada, sodium phosphate and other mild laxatives are ineffectual in controlling the symptoms. Kaolin and mineral oil emulsions definitely aggravate the intestinal symptoms.

I have found no drug to compare with castor oil. An ounce mixed with an equal quantity of orange juice is stirred together with a level teaspoonful of sodium bicarbonate and is given while effervescing. A cleansing enema consisting of two teaspoonfuls of salt to a quart of tap water at a temperature of from 100 to 108 F. will assist materially. If there is much nausea or vomiting it will be necessary to give from 0.0006 to 0.0012 Gm. (from $\frac{1}{100}$ to $\frac{1}{50}$ grain) of atropine hypodermically. The latter dose is usually necessary to produce the desired effect. From fifteen to thirty minutes later the castor oil and enema may be given. Castor oil seems to have little effect on the course of the disease after the first twelve to twenty-four hours.

When the patient begins to eat he should be allowed only a soft bland diet. Acid foods, highly seasoned foods, and foods with a high residue may aggravate the diarrhea or cause its return. McLean [3] advised against the use of milk for children with this condition, but I use it freely for young adults. Water should be given as freely as it is tolerated, but should not be cold. Rest in bed is necessary in the acute phase only, unless other conditions indicate a more prolonged inactivity. I have never known any harm to come from allowing the patient to get up as soon as he felt like it. Complicating subacute appendicitis or the severe colic type of the disease may require that physical activities be restricted for from one to two weeks.

From 4 to 6 capsules (0.15 Gm. each) of heptylresorcinol given with the castor oil, followed by from 2 to 4 capsules taken every four hours

the first day, seems to be of value in helping the castor oil check the symptoms. After twenty-four hours it seems to be ineffectual.

Although sodium ricinoleate is not nearly so effectual as castor oil at the beginning of treatment, from 5.3 to 8 Gm. (from 80 to 120 grains) given daily in divided doses seems to act as a buffer in the intestinal tract against the infection, particularly in the milder cases. I should advise its use if postprandial distress follows the subsidence of the more acute symptoms, with the dose reduced to 0.3 Gm. (5 grains) given four times a day.[38] It seems to lack the laxative effect of castor oil, thus exploding an old theory that the laxative effect of castor oil was due to saponification of its triglyceride of ricinoleic acid.[37] This probably accounts for the fact that sodium ricinoleate cannot replace castor oil in initiating treatment.

For nausea, vomiting and pain from 1.3 to 2 cc. (from 20 to 30 drops) of tincture of belladonna given at once and 1.3 cc. given every four hours perorally is of value. If this is vomited one may resort to atropine given hypodermically. Ethyl aminobenzoate, sodium bicarbonate and peppermint appear ineffectual, although peppermint is sometimes given with belladonna as a flavor and adjuvant because it is claimed to relax gastric peristole. Benzyl benzoate is often disagreeable, although it is flavored with almond oil. This drug and calcium *o*-benzyl-oxybenzoate are often vomited before they have a chance to take effect on the vomiting and distress. Sodium nitrite, given in doses of from 0.06 to 0.18 Gm. (from 1 to 3 grains), may help to control nausea but may increase dizziness. It affects abdominal distress to a lesser extent than the other drugs mentioned or not at all, suggesting that the distress is not due entirely to a spasmodic condition.[38] I used nitroglycerin on only one occasion. Codeine in doses of 0.06 Gm. (1 grain) is a valuable adjuvant to the atropine, particularly if there is pain. A hot water bottle at a temperature of 120 F. or an electric heat pad is useful for the pain but may increase the nausea. In the colic type, rapid relief is obtained with atropine, codeine and heat, followed in from fifteen to thirty minutes by a salt water enema. The patient should be warned that he may be slightly more nauseated for a while after the enema. The administration of mineral oil or its emulsions to patients with constipation is to be discouraged, since they may increase the flatulence and distress.

Although I have given much calcium carbonate, I am not convinced that it has any value in the diarrhea of this condition, but it may be

37. Sollmann, T.: A Manual of Pharmacology, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 210.

38. Beams, A. J.: Nitrites in Spasmodic Conditions of Gastro-Intestinal Tract, J. A. M. A. **97**:907 (Sept. 26) 1931.

given in doses of 2 Gm. (½ drachm) every four hours. The same is true of bismuth subcarbonate. Bismuth subnitrate seems to excel bismuth subgallate; possibly this is due to the nitrate ion, if Steiglitz [39] is correct in his theory of the fate and action of the drug in the intestine. Bismuth subnitrate is given in doses of from 1 to 2 Gm. (15.4 to 30.8 grains) every two to four hours. I usually give 2 Gm. every two hours until the diarrhea is checked, and then every four hours for a full day. I have never noticed any untoward effects from bismuth in such doses in cases of this type. With this I give camphorated tincture of opium in doses of 4 cc. (1 drachm) not oftener than every four hours. If these drugs are given before the end of the second day the diarrhea seems to be prolonged and the cramps worse.

For dizziness, a snugly applied scultetus abdominal binder or adhesive strapping is most effective. One cubic centimeter (15 drops) of epinephrine hydrochloride given hypodermically usually gives relief. If it does, 0.02 Gm. (⅓ grain) of ephedrine should be given every four hours until 4 p. m. If it is given after that time, it may cause sleeplessness in some patients. For nervousness and restlessness, which are common in the neurocirculatory type of the disorder, I have found phenobarbital useful in doses of from 0.015 to 0.03 Gm. (from ¼ to ½ grain) given four times daily, and for insomnia a single dose of from 0.06 to 0.18 Gm. (from 1 to 3 grains) given just before bed time is effective.

Acetylsalicylic acid in doses of from 0.3 to 1 Gm. (from 5 to 15 grains) is the most useful remedy for headache. Although I have used the ice-cap, I doubt the advisability of its use, particularly if there are respiratory symptoms. The nose and throat should be treated as indicated in patients with respiratory symptoms.

MORBIDITY

That this disease is becoming a public health problem of first magnitude is indicated by the widespread reports coming to me through the United States Public Health Service and other sources. The importance of the disease has become rapidly apparent in summer camps and national parks and in institutions such as colleges. Even in these groups the magnitude of the problem is not always appreciated. In spite of the easy access of patients to my service at all times, surveys indicate that I probably saw only about one fifth of the cases which occurred during the local epidemics and that at least from one third to one half or more of the student body is affected annually. In the general population the significance of the disorder is rapidly lost on account

39. Steiglitz, E. J.: Bismuth Subnitrate in Treatment of Arterial Hypertension, J. A. M. A. **95**:842 (Sept. 20) 1930.

of the few persons who seek medical advice because of it. How often have I heard: "It's just something I ate" or "It's only indigestion." This attitude has doubtless been a factor in increasing the mortality from appendicitis.[40] So long as there exists so generally a condition which never seems to kill, in spite of the acuteness of the symptoms, is it not natural that a careless attitude should be engendered? Efforts to educate the public must be redoubled. Physicians must attempt to make a rapid and accurate diagnosis of Spencer's disease in order to prevent unnecessary surgical measures and must try to discover some method of effectively controlling the morbidity.

SUMMARY

There apparently exists quite generally a clinical entity which has erroneously been called gastro-intestinal influenza, food poisoning, ptomaine poisoning, biliousness, acute autointoxication, dietary indiscretion and the like. Considerable information concerning the etiology, epidemiology, pathogenesis, symptomatology and differential diagnosis of this condition has been gathered from observations on more than a thousand cases seen within the past seven and a half years. A distinctive name is now proposed. The present report is based on a study of about 750 college students who had from one to six or more attacks between September, 1927, and June, 1932. Much more work is needed to settle some points, particularly those concerning the etiologic agent and the pathologic condition which it produces.

40. Bower, J. O.: Mortality of Acute Appendicitis, J. A. M. A. **99**:1765 (Nov. 19) 1932. Lowe, H. A.: Causes of High Mortality in Appendicitis, J. Missouri M. A. **28**:525, 1931.

UNCOMPLICATED SYPHILITIC AORTITIS

DIAGNOSIS, PROGNOSIS AND TREATMENT

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The questions of diagnosis and of prognosis of untreated syphilitic aortitis with aneurysm or aortic regurgitation require no elaboration. Two reports from this clinic [1] have shown that by appropriate treatment of these conditions, it is possible materially to prolong life and to alleviate symptoms in a considerable proportion of cases. In these reports and elsewhere, the *a priori* opinion has been offered that the results of treatment should be even more satisfactory if treatment could be administered while the aortitis was still uncomplicated by valvular incompetency or aneurysmal sacculation. A demonstration of this fact, if true, depends, however, on the accuracy of diagnosis of uncomplicated aortitis.

Although it has been generally agreed that this diagnosis could be made occasionally in a patient with fully developed symptoms and signs, and although some clinicians, as for example Albutt,[2] have insisted that it might be made with far greater frequency than is customary, there is still a prevalent impression that in the absence of aneurysmal dilatation or aortic insufficiency, syphilitic aortitis cannot be recognized with accuracy during life. The skepticism is of course due to the

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital.

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1. Moore, J. E., and Danglade, J. H.: The Treatment of Cardiovascular Syphilis: A Study of the Duration of Life in 141 Treated and Untreated Patients with Aortic Regurgitation and Aneurysm, Am. Heart J. **6**:148, 1930. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Treatment of Cardiovascular Syphilis: Results Obtained in Fifty-Three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation, Arch. Int. Med. **49**:879 (June) 1932.

2. Allbutt, T. C.: Diseases of the Arteries, Including Angina Pectoris, New York, The Macmillan Company, 1915.

similarity of symptoms and physical signs resulting from syphilitic aortitis, aortic atherosclerosis and essential hypertension.

In an earlier communication,[3] one of us (J. E. M.), with Danglade and Reisinger, discussed the diagnosis of uncomplicated syphilitic aortitis on the basis of a study of the correlation of clinical and pathologic findings in 105 patients in whom the existence of this lesion had been recognized during life in only a few, but proved at postmortem examination in all. Seven diagnostic criteria were listed: (1) teleradiographic and fluoroscopic evidence of aortic dilatation; (2) increased retromanubrial dulness; (3) a history of circulatory embarrassment; (4) a tympanitic bell-like, tambour accentuation of the aortic second sound; (5) progressive cardiac failure; (6) substernal pain, and (7) paroxysmal dyspnea. The belief was expressed that in a patient with a recognized late stage of syphilis (whether or not the Wassermann reaction of the blood is positive) without disease of the mitral valve, the presence of any three of these criteria is strong evidence in support of a definite diagnosis of uncomplicated syphilitic aortitis, while the presence of any two of them renders the diagnosis probable.

We realized that in order to validate this position it would be necessary to follow a series of patients in whom this diagnosis had been made during life, in order to determine to what extent the more definite lesions of aneurysm or aortic regurgitation developed, the cause of death, and the effect, if any, of treatment on the course of the disease. The subject matter of the present communication is a consideration of these points.

OBSERVATIONS

The Material of the Study.—We report on the status of 115 patients with a late stage of syphilis in whom the clinical diagnosis of syphilitic aortitis was made. Each of these patients was examined by several observers, and the majority by one of us. We limit ourselves to a discussion of three main points: (1) the extent to which the ultimate outcome justified the original diagnosis; (2) the extent to which the outcome was influenced by treatment, and (3) the influence of associated hypertension on the outcome. Because of lack of space we omit a consideration of the evidence on which the diagnosis of uncomplicated syphilitic aortitis was based in these 115 patients. This will appear in a later communication. At present it must suffice to say that all of them were definitely syphilitic, that none had disease of the mitral valve, and that all had at least two, and most of them more, of the seven diagnostic criteria listed.

3. Moore, J. E.; Danglade, J. H., and Reisinger, J. C.: Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm: Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients, Arch. Int. Med. **49**:753 (May) 1932.

Validity of the Diagnosis of Uncomplicated Aortitis as Determined by the Subsequent Course.—We have made every effort to follow these patients with frequently repeated physical and roentgen examinations. Those who regularly attended the clinic have been reexamined at periodic intervals; others have been persuaded by the efforts of social service to return for study. Deaths have been verified by examination of the records of our own and of several other of the large hospitals in Baltimore and of the death certificates issued by the City Health Department. The success of this type of follow-up is apparent from the fact that of the 86 living patients, none has been under observation for less than two years, and the average period of observation exceeds eight years.

If in a patient with a diagnosis of uncomplicated aortitis—the existence of saccular aneurysm or aortic regurgitation having been

TABLE 1.—*Outcome in 115 Patients with Uncomplicated Syphilitic Aortitis (Without Reference to Treatment)*

	Living			Dead			
Total Number Cases	Symptom-Free; No Progress in Physical or Roentgen-Ray Signs	Showing Progress in Symptoms or Signs	Showing Development of Aortic Regurgitation or Aneurysm	Of Aneurysm or Aortic Regurgitation	Of Other Forms of Cardiovascular Syphilis (Proved)	Probably of Cardiovascular Syphilis	Of Other Known or Unknown Causes
115	41	35*	10†	7	2	6	14‡

* Of these patients, 7 are wholly or partly incapacitated by progressive cardiac failure.
† In 2 instances the clinical diagnosis is questionable.
‡ In 3 patients aortic regurgitation developed before death.

excluded by all available means—one of these two conditions subsequently develops, it may be assumed that the original diagnosis of aortitis was correct, whether or not the lesion is verified at section. If aneurysm or aortic insufficiency does not develop, the only absolute proof of the correctness of the original diagnosis is the evidence of necropsy. Strong presumptive proof, however, is offered if the symptoms and physical signs originally present increase in severity and extent, and particularly if congestive heart failure for which there is no other obvious explanation develops.

During the period of this study, the outcome in our 115 patients, leaving out of consideration for the moment the amount of treatment administered, is as shown in table 1. In 22 of the total number, or 19.1 per cent, indubitable evidence of cardiovascular syphilis developed, testifying to the correctness of the original diagnosis. In these, saccular aneurysm developed in 8 (2 now living, 6 dead) and aortic insufficiency in 12 (8 still living, and 4 dead); 2 others, who died of congestive heart failure, were found at necropsy to have syphilitic aortitis complicated by myocarditis.

Presumptive evidence of the validity of the original diagnosis is furnished by 41 additional patients, or 35.6 per cent. Of these, 6 died elsewhere than under our observation of some form of disease of the heart variously diagnosed by the attending physician, within an average interval of thirty months after the diagnosis of aortitis had been made, i. e., within so short a time that, considering the demonstrated absence of any form of heart disease other than cardiovascular syphilis at the time of the original examination, death may be presumed to have occurred from that cause. Thirty-five are still living in whom symptoms, or more commonly physical or roentgen ray signs, originally present have grown more marked, and of these, 7 are wholly or partly incapacitated by progressive cardiac failure.[4]

Thus, the original diagnosis seems thoroughly justified by virtue of the fact that, disregarding the amount of treatment given, there has been definite or presumptive evidence of progression of the lesion in 54.7 per cent of the 115 patients studied. This portion of the study is confirmatory of our already expressed conclusion, based on a correlation of necropsy and clinical findings,[3] that the diagnosis of syphilitic aortitis can be accurately made in a considerable proportion of cases, even in the absence of aortic regurgitation or aneurysm.

Results of Treatment in Uncomplicated Syphilitic Aortitis.—In table 2 appear the results of treatment of patients with uncomplicated aortitis, subdivided into two groups on the basis of the amount of treatment given. The outcome is expressed in the simplest possible terms to show the mortality rate (including deaths from all causes) and the number of patients in each group in whom incontrovertible clinical evidence of cardiovascular syphilis had developed in the form of aortic regurgitation or saccular aneurysm, or who had certainly or probably died of cardiovascular syphilis. The data indicate that untreated or inadequately treated syphilitic aortitis offers a grave prognosis. It also appears that aneurysm or aortic regurgitation (especially the latter) may develop in spite of adequate treatment (8 of 47 patients in the best treated group). This is not surprising. Indeed, in some instances it is probable that the development of aortic regurgitation is actually hastened by treatment. The valve leaflets may already be involved by the inflammatory process, but not yet be so distorted as to produce incompetency, before treatment is begun. With the healing effect of treatment, inflammation is replaced by scar tissue, and distortion and subsequent valvular incompetency appear earlier than would

4. The fact that cerebral hemorrhage was the cause of death in 4 of the 14 patients recorded as dying of some other cause than cardiovascular syphilis exemplifies the frequent association of syphilitic aortitis with a more generalized syphilitic vascular involvement.

otherwise have been the case. This is not, however, necessarily disastrous. As Stokes [5] has aptly put it, a progressive disability is exchanged for a static one.

The average duration of life dating from the time of the diagnosis of aortitis, in the living well treated patients of this series, exceeds eight years, as compared with the average of somewhat over five years for a similarly treated group of patients with aneurysm or aortic regurgitation. Many more of the patients with uncomplicated aortitis are free from symptoms and able to work than are those in the earlier group. It seems certain from our data that the treatment of uncomplicated syphilitic aortitis relieves symptoms, maintains physical efficiency, prevents the appearance of graver forms of cardiovascular syphilis and prolongs life in a considerable proportion of cases. By

TABLE 2.—*Relationship of Antisyphilitic Treatment to the Outcome of Uncomplicated Syphilitic Aortitis*

Treatment	Total No. of Patients	Deaths, All Causes		Incidence of Graver Forms of Cardiovascular Syphilis (Aneurysm, Aortic Insufficiency or Death from Congestive Heart Failure), Certain or Probable	
		Patients	Per Cent	Patients	Per Cent
Fewer than 12 injections of an arsphenamine product with heavy metal preparation in interim	45	19	42.2	14	31.1
More than 12 injections of an arsphenamine product with heavy metal preparation in interim	70	10	14.2	14	20.0

comparison with the results of treatment in patients who have already developed aneurysm or aortic regurgitation, the results in uncomplicated aortitis are vastly better.

Influence of Essential Hypertension Complicating Syphilitic Aortitis on the Outcome.—On the basis of numerous studies, it is clear that hypertension is not caused by syphilitic aortitis, and that the association of the two conditions is relatively infrequent. As a matter of fact, essential hypertension occurs in patients with aortitis with about the same frequency as in nonsyphilitic patients in groups of analogous age. We discussed elsewhere [3] the diagnostic difficulties which arise when the two conditions are associated, and concluded that in spite of their coexistence the diagnosis of syphilitic aortitis may often be made with accuracy. This statement receives confirmation from the present study, which also provides another fact of importance, i. e., that the prognosis in syphilitic aortitis is much worse when hypertension from any cause

5. Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1926.

is a complicating feature. These data appear in table 3. Of the total 115 patients with uncomplicated aortitis, 31 had hypertension (systolic pressure, 150 or over), 74 did not, and regarding 10, information is lacking. In the group with hypertension, aneurysm or aortic regurgitation subsequently developed in 10 (32 per cent). In those without hypertension, this occurred in 9 (12 per cent). The mortality rate and the incidence of the graver forms of cardiovascular syphilis are approximately twice as great in patients with, as in patients without, a complicating hypertension.

TABLE 3.—*Influence of Hypertension on the Outcome of Uncomplicated Syphilitic Aortitis*

	Total Number of Cases	Mortality, per Cent	Percentage of Incidence of Cardiovascular Syphilis (Aneurysm, Aortic Regurgitation or Death from Congestive Heart Failure), Certain or Probable
Patients with hypertension	31	32.2	35.4
Patients without hypertension	74	19.0	17.5
Patients with no data as to hypertension	10	50.0	40.0

SUMMARY AND CONCLUSIONS

1. By uncomplicated syphilitic aortitis is understood a diffuse supravalvular involvement of the aortic wall, with or without diffuse dilatation, but without valvular incompetency or saccular aneurysm.

2. Seven criteria for the clinical diagnosis of this condition are listed.

3. The accuracy of clinical diagnosis has been tested by the prolonged study of 115 patients in whom this diagnosis had been made during life.

4. In 19.1 per cent of this group of patients, indubitable graver forms of cardiovascular syphilis subsequently developed, and in an additional 35.6 per cent, presumptive evidence of the correctness of the original diagnosis was furnished by the subsequent course.

5. The clinical diagnosis of uncomplicated syphilitic aortitis can be accurately made in a considerable proportion of patients with late syphilis.

6. A consideration of the results of treatment indicates that symptoms may be relieved, physical efficiency maintained, the appearance of the graver forms of cardiovascular syphilis prevented, and life prolonged in a considerable proportion of patients with uncomplicated aortitis, and that these results are better than those obtainable after the development of aortic regurgitation or aneurysm.

7. Hypertension complicating syphilitic aortitis doubles the mortality rate and the incidence of development of the graver forms of cardiovascular syphilis.

Correspondence

MODIFIED DEXTROSE TOLERANCE TEST

To the Editor:—In the July, 1933, issue of the ARCHIVES, page 147, appeared an article by Dr. H. T. Ricketts, "An Appraisal of the Modified Dextrose Tolerance Test," which contains a number of misleading statements on which I should like to comment.

1. In an article, entitled, "Modification of the Dextrose Tolerance Test as an Index of Metabolic Activity of the Liver," by Lewis Gunther, John B. Lagen, William J. Kerr and me (ARCH. INT. MED. **46**:482 [Sept.] 1930), we claim that a modification of the dextrose tolerance test produces lower blood sugar values in patients with hepatic disease than in normal persons; this is substantiated by the figures of Dr. Ricketts. His graphic chart shows that, with two exceptions, the lowest blood sugar value in the curves of patients with hepatic damage is lower than the lowest figures in the normal and "doubtful" groups. The first exception (*11*) is in a case of carcinoma of the pancreas with obstructive jaundice, and we think that it is an advantage of the test that jaundice without intrinsic injury to the liver gives negative results. The other exception (*14 a*) is a second test in a patient who recovered and whose galactose tolerance and excretion of bromsulphalein had returned to normal.

2. Our dividing line between normal and abnormal cases "in the vicinity" of 70 mg. per hundred cubic centimeters with the Folin and Wu method was selected empirically from a study of sixty-four cases on the basis of clinical findings and the rose bengal dye excretion test. If Folin's new method of blood sugar determination is used, the dividing zone must again be established empirically, and not by simple subtraction of 20 mg., because this method excludes noncarbohydrate-reducing substances of the blood. Quantitatively, by far the most important of these substances is glutathione, which has been shown to increase in the blood of normal persons following injections of insulin (Cahane, M.: *Comp. rend. Soc. de biol.* **110**:644, 1932) and to be diminished in the blood of patients with many hepatic diseases, such as jaundice and cirrhosis (Binet, L., and Arnaudet, A.: *Comp. rend. Soc. de biol.* **110**:24, 1932; Villaret, M.; Justin-Besançon, L.; Even, R., and Drilhon, M.: *Bull. et mém. Soc. méd. d. hôp. de Paris* **48**:775, 1932; Varela, B.; Munilla, A., and Duomarco, J.: *Comp. rend. Soc. de biol.* **111**:533, 1932). Consequently, the results of the modified dextrose tolerance test may be rendered more decisive by using a method of blood sugar determination, such as the Folin and Wu method, which includes in its readings variations of glutathione, because, as indicated by the cited references, such variations in many hepatic diseases enhance the changes in blood sugar during the test. From Dr. Rickett's cases an empirical dividing line for the new Folin method suggests itself at about 30 mg.

At present, a survey of recent cases in which tests of the hepatic function were performed is being made at the University of California Hospital. This survey, so far, reveals agreement of the modified dextrose tolerance test with the clinical picture and with the rose bengal test in twenty-six of thirty patients with and without hepatic disease. In the remaining four cases, the clinical picture is in accord with the modified dextrose tolerance test in two instances and with the dye excretion test in two cases. We consider this as further evidence that 70 mg. is an approximately correct dividing zone if the Folin and Wu method is used. We pay little attention in the interpretation of the test to insulin reactions, because we

have seen the blood sugar of patients with an habitually low blood sugar level reach levels sometimes under 30 mg. without reactions, while the reverse is true for patients with an habitually high blood sugar level.

3. A just criticism of the test from Dr. Ricketts' blood sugar curves might be that the "spread" between normal and pathologic cases is not great enough; on the one hand, the five patients with the lowest blood sugar in the normal and "doubtful" groups (cases 2, 3, 5, 7 and 9) have conditions such as cardiospasm, chronic vomiting or pyloric stenosis, leading to disturbances of nutrition and low hepatic glycogen, which reduces the ability of the liver to release dextrose in case of impending hypoglycemia, and, on the other hand, in his pathologic cases the patients had only mild hepatic insufficiency, since all but one (case 14) were found to have normal results with a dye excretion test, which is accepted as a valuable diagnostic aid by most medical writers.

4. From a comparison of the bromsulphalein test with the modified dextrose tolerance test in Dr. Ricketts' small number of cases, it is apparent that the latter gave more accurate indications of hepatic damage. At the same time, it is significant that the lowest blood sugar level (11 mg.) was obtained and the test had to be interrupted owing to a marked insulin reaction in the only patient who had an abnormal retention of the dye. Later, when the excretion of bromsulphalein became normal, the lowest blood sugar level following the modified dextrose tolerance test also increased to the level obtained by Dr. Ricketts in his normal cases, and at this time there was no necessity of interrupting the test. This indicates a good agreement between the two tests.

5. In discussing the theoretical aspects of the modified dextrose tolerance test, Dr. Ricketts mentions that the blood sugar curve following the administration of 100 Gm. of dextrose may end in hypoglycemia in normal persons and that therefore the giving of 50 Gm. of this sugar with 20 units of insulin is even more likely to produce hypoglycemia. The reason for hypoglycemia in the first case is that 100 Gm. of dextrose is a heavy strain on the sugar-assimilating organs which are stimulated to utilize increased amounts of dextrose from the blood. When the 100 Gm. given is used up, overfunctioning of these organs still goes on, so that temporary hypoglycemia results. On the contrary, 50 Gm. of sugar covered by 20 units of insulin represents a comparatively light load which causes a much lesser stimulation of the sugar-assimilating organs.

We realize that opinions as to the clinical usefulness of our test may differ, especially since it is based on carbohydrate metabolism in which several extrahepatic factors play an important part, but we cannot pass in silence a denial of the fundamental facts involved. This is especially so since our clinical work was substantiated by Morawitz and Mancke (*Klin. Wchnschr.* **11**:623, 1932), who also performed the test on fifteen normal persons, and by Milbradt (*Arch. f. Dermat. u. Syph.* **164**:399, 1931), who, among a hundred cases, tested ten patients without hepatic disease. In addition, our clinical findings were duplicated in animals with experimental injury to the liver (ARCH. INT. MED. **50**:58 [July]; 257 [Aug.] 1932).

T. L. ALTHAUSEN, M.D., San Francisco.

To the Editor:—My contention (ARCH. INT. MED. **52**:147 [July] 1933) that the modified dextrose tolerance test is not a satisfactory measure of the metabolic function of the liver was based on results obtained by performing this test on ten patients who were considered to have normal livers and on four patients with frank hepatic disease. In nine of the ten normal patients, definite chemical and clinical hypoglycemia developed—the response said by Dr. Althausen to be characteristic of disease of the liver. Three of four of the patients with hepatic disease also

exhibited a terminal drop in blood sugar which was somewhat, but not markedly, lower than in most of the normal cases. There was, therefore, no essential difference between the behavior of the normal and the abnormal groups.

The important criticisms of this work which are raised in Dr. Althausen's present communication revolve about two questions: 1. Were the patients normal? 2. What constitutes hypoglycemia?

1. The "normal" group consisted of patients on the gastro-intestinal service of the Billings Hospital who were being treated for conditions in no recognized way related to the liver and who gave no evidence of hepatic disease. Dr. Althausen's assumption that these patients must have had a low hepatic glycogen simply on the basis of their diagnoses is unwarranted. In accordance with the technic which he originally proposed, all patients in this group had been consuming for several days before the test an adequate diet, which contained from 250 to 300 Gm. of carbohydrate. The group as a whole averaged only 7.6 per cent underweight as computed from the tables of Davenport (Body Build and Its Inheritance, Washington, D. C., Carnegie Institution, 1923, publ. no. 329). This can scarcely be called a pathologic deviation. The patient in case 5 (one of nervous vomiting), whose blood sugar dropped to 25 mg. per hundred cubic centimeters, was slightly above normal weight as given by these tables. In none of these patients had there been any acute loss of weight.

It might be added here that so far as the degree of hepatic insufficiency in the pathologic cases is concerned, all of the patients, regardless of the dye excretion test, had suffered damage to the liver sufficient to produce jaundice, which in only one case was due to obstruction.

2. In the original paper by Dr. Althausen and his associates the proposition was made that "terminal hypoglycemia under the conditions of the test meant injury of the liver." Using the Folin and Wu method of analysis, they placed the dividing line between normal and hypoglycemic values at 70 mg. of sugar per hundred cubic centimeters of blood. The new Folin method which I used gives values about 20 mg. lower, so that the dividing line was placed at 50 mg. per hundred cubic centimeters of blood. Dr. Althausen now proposes to apply in my cases a critical level, as determined by the Folin method, of 30 mg. per hundred cubic centimeters of blood. He would thus seem to imply either that the blood sugar must drop to 30 mg. before hypoglycemia may be considered to exist, or that he has abandoned the hypoglycemic concept in this connection altogether. That any normal person in whom a blood sugar of from 30 to 50 mg. develops (Folin method) is in a state of hypoglycemia would seem obvious. If, on the other hand, Dr. Althausen and his colleagues have decided not to use the term "hypoglycemia" in referring to responses of patients with hepatic disease, a statement from them to that effect would be in order.

If the modified dextrose tolerance test depends for its interpretation on estimation of the amount of sugar in the blood, it is difficult to see how Dr. Althausen can justifiably take exception to the use of an analytic method which determines the true blood sugar more accurately than does his own.

With regard to glutathione, investigation of the reference cited by Dr. Althausen to the effect that the amount of this substance in the blood of normal patients is increased by the injection of insulin, yields the following information: Cahane gave 20 units of insulin to two healthy human subjects and followed the blood sugar and total sulphur content of the blood for two hours after injection (no figures are given for the proportion of the total blood sulphur which glutathione constitutes). The blood sugar dropped as anticipated, but the total sulphur increased in one patient by only 2 mg. per hundred cubic centimeters of blood, and in the

other by 1.6 mg. The remainder of Cahane's work was done on two normal dogs, into each of which he injected from 2.5 to 4 units of insulin per kilogram of body weight—a decidedly large dose—and obtained increases of 0.6 mg. and 2.2 mg. of sulphur per hundred cubic centimeters of blood, respectively. Such results are entirely within the limits of error of the method and have no significance in the present connection. Even taking them at their face value, it is impossible to imagine that differences of from 0.6 to 2.2 mg. of glutathione following the injection of insulin could have any material influence on the very much higher figures in which even hypoglycemic blood sugar values are expressed.

While a disregard of insulin reactions in interpreting tests performed on patients with abnormal blood sugars during fasting is understandable, the presence of normal levels during fasting in my patients establishes the significance of their hypoglycemic symptoms, especially since all reactions were accompanied by blood sugars which were undeniably below normal.

The matter of stimulation of the sugar-assimilating organs by dextrose feeding is one largely of speculation. There is, however, direct evidence that a dose of dextrose of even 50 Gm. given by mouth may produce hypoglycemia. Gibson and Larimer (*J. A. M. A.* **82**:468 [Feb. 9] 1924) gave this amount to a patient with renal glycosuria who had a blood sugar during fasting of 58 mg. Three hours later the patient had mild symptoms, and the blood sugar was found to be 40 mg. Moreover, Stenström (*Deutsches Arch. f. klin. Med.* **157**:216, 1927) "in four patients with blood sugars during fasting between 76 and 95 mg. (noted) hypoglycemia about two hours after they had taken 1 Gm. of dextrose per kilogram of body weight, with readings between 46 and 53 mg." If, then, the administration of as little as 50 Gm. of dextrose alone may be followed by hypoglycemia in normal persons, one might expect that the addition of 1,500 cc. of water and 20 units of insulin would accentuate this tendency. Results in my normal cases substantiate this expectation. In answer to Dr. Althausen, therefore, it might be said either that this dosage of dextrose produces a greater pancreatic stimulation than he assumes, or that possibly the insulin is inadequately covered by the sugar given.

With respect to the confirmation of Dr. Althausen's work by other investigators, Morawitz (in whose clinic Dr. Althausen did some of his work) and Mancke give only the average curve for their normals. Their results would be more convincing had they given figures for the individual cases, for a functional test is useful only to the extent that all normal persons can be shown always to respond to it in the same way. Morawitz and Mancke, moreover, accept as a normal reaction a maximum difference of 20 mg. between the blood sugar level during fasting and the lowest blood sugar level. All but three of my normal patients showed differences considerably greater than this. Milbradt, like the authors just mentioned, merely makes a statement about the average of his ten normal patients.

The data obtained by Dr. Althausen on laboratory animals are inconclusive. Reference is made to the article, entitled, "Influence on Carbohydrate Metabolism of Experimentally Produced Hepatic Changes: III. Chloroform Poisoning" (ARCH. INT. MED. **50**:257 [Aug.] 1932), in which are given the results of the administration of the modified dextrose tolerance test to rabbits. This test was performed on nine normal rabbits before they were poisoned. Of this number, four (rabbits 804, 824, 832 and 835) responded by a drop in blood sugar of 86, 47, 68 and 50 mg., respectively, from the initial level at the end of three hours. Incidentally, these drops in some cases were greater than those obtained after poisoning, although the initial blood sugar levels were lower in the latter instance. I cannot discover that Dr. Althausen has set up a dividing line between "normal" and "abnormal" responses for rabbits, but such results in normal animals are entirely consistent with mine in normal human beings.

In conclusion, it is evident from both Dr. Althausen's work and my own that the modified dextrose tolerance test usually produces hypoglycemia in hepatic damage. The difficulty is, however, that, in my own hands at least, it also produces hypoglycemia in patients who have normal livers, a fact which has recently received confirmation by Migneco (*Policlinico* **101**:248 [July 15] 1933), who also concluded that the test was not satisfactory. A comparison of the statements made in Dr. Althausen's original article (ARCH. INT. MED. **46**:482 [Sept.] 1930) with those contained in his present communication reveals that in the former he refers to "hypoglycemia" as the criterion of hepatic damage, whereas in the latter he merely states that the modified dextrose tolerance test "produces lower blood sugar values in patients with hepatic disease than in normal persons." If the last statement quoted is to be taken at its face value, with no further implications, it represents, granting further substantiation, an interesting contribution to the already existing knowledge of disturbed carbohydrate metabolism in hepatic disorders. If, however, the modified dextrose tolerance test is to be set up as a clinical procedure, with hypoglycemia "under the conditions of the test" as the sine qua non for hepatic damage, its usefulness is apt to be largely vitiated by the marked tendency of normal persons to respond by blood sugar levels which are definitely hypoglycemic.

HENRY T. RICKETTS, M.D., Chicago.

To the Editor:—After reading Dr. Ricketts' reply to my first letter, I am constrained to make the following further comments:

1. Cahane's work, far from being "within the limits of error," is a confirmation of the work of Zunz (*Compt. rend. Soc. de biol.* **108**:223, 1931).

The rise in glutathione after the injection of insulin in Cahane's work is *not* from 0.6 to 2.2 mg., as stated at the end of the paragraph by Dr. Ricketts, but over ten times that amount (the sulphur coefficient of glutathione is 10.5). In the two human cases this difference amounts to 16 and 22 mg. and is of considerable importance.

2. As to the production of hypoglycemia in *normal* persons with 50 Gm. of dextrose: In the case of Gibson and Lorimer, Dr. Ricketts omitted the important fact that this patient had spontaneous attacks of hyperglycemia with subjective symptoms. Furthermore, this patient had marked renal glycosuria with a blood sugar during fasting of 58 mg. We reported a similar case and pointed this condition out as a source of error in the modified dextrose tolerance test (*Arch. f. klin. Med.* **170**:294, 1931).

Stenström's work was *not* done on normal persons as stated by Dr. Ricketts, but on persons with pluriglandular disturbances (thyroid, ovaries and suprarenals). Two other patients in the same series of six cases had spontaneous attacks of hypoglycemia, in one case with coma for over twenty-four hours. In addition, one of the four cited patients again had renal glycosuria.

3. How convincing the results of Morawitz and Mancke are can be judged from their curves (chart).

Milbradt does *not* "merely make a statement about the average of his normal patients" but specifies that *all* of his ten normal patients had a negative reaction to the test. Since Dr. Ricketts gives no credence to the statements of these investigators, we fail to see how their individual data would be more reliable.

4. It is common knowledge that the sugar metabolism of rabbits is less stable than that of man, and we are content to let our data on laboratory animals speak for themselves. We also wish to point out that Dr. Ricketts arbitrarily selected for criticism one acute experiment with chloroform, omitting to mention two experi-

ments with phoshporus. Of the three experiments, the one with chronic phosphorus poisoning is the most significant one in regard to clinical application.

5. I am unable to discuss the results of Migneco since I cannot find his article under the given reference.

T. L. ALTHAUSEN, M.D., San Francisco.

To the Editor:—1. The test proposed by Dr. Althausen is a test of dextrose tolerance. The method of blood sugar analysis which I used determines dextrose, and largely eliminates other reducing substances which might obscure the true picture of dextrose metabolism. The subject of glutathione, therefore, is irrelevant to this discussion, and it already has received more attention than it deserves. It is necessary, however, to reply to Dr. Althausen's last statements in this connection.

(*a*) All workers in this field are by no means agreed as to whether insulin produces augmentation of the sulphydryl bodies in the blood. Zunz remarks that Tateishi (*Kyoto-Ikadaigaku-Zasshi* **5**:51, 1931) demonstrated sometimes a decrease of glutathione in healthy human subjects after injection of insulin, and both Cahane and Zunz refer to the work of Blanchetière, Binet and Mélon (*J. de physiol. et de path. gén.* **27**:1 and 19, 1929), who are said to have observed no influence of insulin on the concentration of glutathione and thionine in the blood. Other investigators did not confirm these results.

(*b*) My figures taken from Cahane's results, showing an increase of only 0.6 to 2.2 mg. of *total sulphur* per hundred cubic centimeters of blood after injection of insulin, are correct as given. In the two human cases the increase was 1.6 and 2.2 mg., respectively. Dr. Althausen, in stating that the increase in glutathione was over ten times these figures (because its sulphur coefficient is 10.5), apparently makes the mistake of assuming that all of the blood sulphur is glutathione sulphur, which obviously it is not. Cahane indeed did not determine glutathione as such, and therefore offers no evidence that its level was changed at all.

(*c*) Cahane stated that the total blood sulphur reaches its height in from one-half to one and a half hours after the administration of insulin and returns to normal at the end of two hours. Thus, at the crucial point in the modified dextrose tolerance test, when hypoglycemia is most marked (at the second to third hour period), the rise in total sulphur produced by insulin has, according to this author, disappeared.

(*d*) Zunz, who did determine glutathione, and whose results Cahane is alleged to have confirmed, found in dogs a considerable variation in the time of appearance of the glutathione peak and in the time of its return to normal after the administration of insulin. He does not mention the occurrence of a peak at two or three hours. This author stated: "In general, insulin tends indeed to augment the reduced glutathione content of arterial blood, but this increase represents ordinarily only 2 to 7 mg., and only exceptionally reaches 10 to 12 mg., per hundred cubic centimeters of blood" (previous citation, p. 224).

(*e*) When one considers the facts that insulin produces only such questionable or slight rises in glutathione as previously brought out, that this substance in the concentration in which it exists in normal blood has only about 25 per cent of the reducing power of dextrose as determined by the Folin method * and that increased amounts of it at a time from two to three hours after the injection of insulin are either minimal or entirely absent, Dr. Althausen's attempt to explain my results on the basis that glutathione is eliminated by the analytic method which I used becomes fruitless.

2. Although the possibility exists that the mild subjective symptoms which the patient of Gibson and Larimer experienced at home were due to hypoglycemia, this was never proved by blood sugar determinations made at such times.

Dr. Althausen has given a grossly inaccurate idea of Stenström's work. The diagnoses in three of the four cases cited were as follows:

Case 1: "Neurasthenia and edema fugans."

Case 2: "Neurasthenia and transitory glycosuria."

(Glycosuria, said to have been found one week previously, was absent in both control determinations. Blood sugar readings for five consecutive half hour intervals during the test were 95 [fasting], 175, 156, 111, 55 and 46, with an excretion of only 0.95 Gm. of sugar in the urine. A diagnosis of renal glycosuria from such findings cannot be established.)

Case 3: "Neurasthenia."

Nowhere does Stenström give the slightest evidence that any of these patients had pluriglandular disturbances.

Case 4 was that of a young woman in whom hypoglycemia developed after the ingestion of 47 Gm. of dextrose. She gave a history of amenorrhea of seven months' duration and was found to have a low blood pressure, a palpable thyroid and a basal metabolic rate of —9 per cent. Stenström, instead of implying that a pluriglandular syndrome was present in this patient, conservatively stated: "Aside from the cessation of the menses, the symptoms of an endocrine disturbance are extremely slight, but the possibility of a pluriglandular disturbance, even in a very mild form, can be excluded" (*Deutsches Arch. f. klin. Med.* **157:** 223, 1927). The two patients with spontaneous hypoglycemia referred to by Dr. Althausen were not subjected to the dextrose tolerance test and have no place in this discussion.

3. The curves of averages given by the German investigators do not prove that *each* of their normal patients responded to the test by maintaining the blood sugar at nonhypoglycemic levels. The just and time-honored right to demand protocols in scientific investigation has not yet been abrogated.

4. Regarding Dr. Althausen's animal experiments, the marked drop in blood sugar produced by the modified dextrose tolerance test in four of nine rabbits which were used as *normal controls* clearly has nothing to do with the kind of poison which was given later. Moreover, protocols of experiments on normal rabbits published in another article (Althausen and Thoenes: Arch. Int. Med. **50:**46 [July] 1932) show similar decreases in blood sugar after the test in several animals, some of which were used later in the experiments with phosphorus.

If the experiment with chloroform will not bear criticism, it should not have been cited by Dr. Althausen as confirming his clinical results.

The instability of the sugar metabolism of rabbits only goes further to cast doubt on the application to man of results so obtained.

5. The previous reference to Migneco's article was incorrect. The figures given referred to the abstract which appeared in *The Journal of the American Medical Association.* The original article will be found in *Policlinico* (**40:**845 [May 29] 1933).

*Koch, F. C.: Personal communication to the author. Laked blood was dialyzed until free from reducing substances when tested by the Folin copper method. Known amounts of glutathione were added to such laked blood and the reducing value in terms of dextrose determined by the Folin copper method on the tungstate blood filtrates.

Henry T. Ricketts, M.D., Chicago.

Book Reviews

Clinical Science, Incorporating Heart. Edited by Thomas Lewis, M.D., F.R.S. Volume 1. Number 1. Pp. 258. London: Shaw & Sons, Ltd., 1933.

In the letter which accompanies the first number of *Clinical Science*, Messrs. Shaw and Sons remind one that the journal *Heart* was started just twenty-four years ago. "At that time cardiac problems were being studied with unusual intensity, and a journal specially designed to publish original work dealing with the physiology and pathology of the cardio-vascular system had become a necessity to workers in that field. *Heart* successfully fulfilled that purpose. Even at its conception it was realized that in the course of time the flow of original work would diminish and the rate of publications decline. It is now felt that the time has arrived to widen its scope in order to maintain its standards of publication." Whether or not one agrees with the attitude of Messrs. Shaw, the idea of restricting the field of highly specialized medical journalism stimulates reflections. To begin with, every worker in medicine must agree that the number of publications has assumed such magnitude as in itself to constitute a serious problem. To read all the journals, or even to skim them, is physically impossible, and one looks forward to their arrival not with pleasure but with despair. If this colossal mass of material represented in large part new and valuable additions to knowledge, or even the results of genuine endeavor, one would be forced to be patient, if not pleased; unfortunately much of what is printed adds nothing either to ideas or to knowledge, and considerable is beneath criticism or even contempt. The causes of this state of affairs are not far to seek if one analyzes the contents of current journals. The most vicious type of paper is that which is produced merely for the purpose of bringing the author into print. Why editors admit to their pages essays obviously compounded from standard textbooks or reports of cases in which nothing new is brought out remains a mystery. Another type of article, especially prevalent at present, is that which "gilds the lily." Here material which is familiar to all is restudied, and the results are expressed in mathematical terms. The principle is a sound one since the quantitative evaluation of biologic data is of undoubted value, but the opportunities for exploitation are enormous. Finally there are those contributions which are, to be sure, original but in which no rational question is asked or useful answer produced; the reviewer recalls the incident of the weary professor who said to the student plaguing him for a topic for research, "Get some blood from mice and analyze it for arsenic; that's never been done before."

Another problem which confronts harassed editors is that of the manner rather than the matter of the manuscript. Infelicity of style and even bad grammar may be passed over, but the common practice of extending to twenty or more printed pages what could be adequately said in five or six is inexcusable. "The greatest possible number of words is used to express the smallest quantity of ideas," and the essence of the thesis after being anticipated in the introduction is labored in the body of the paper, recapitulated in tables, resummarized in the discussion and finally exposed yet again in the conclusions. Space is often wasted with bibliographies which are long but serve no real purpose, since they are not definitive, and with undue detail as to method. As a rule original work can be adequately presented in from five to fifteen pages; if more space is necessary, the subject is usually multiple and should be divided into several communications.

In the ardor of stating the case against certain vices of medical journalism, the reviewer must hasten to say that none of the criticisms applies to the new journal. The entire contents of the number emanate from the medical unit or

from the department of clinical research of University College Hospital. A variety of topics is dealt with: the physiologic action of insulin, pain derived from the skin, the action of digitalis, angina pectoris and renal function. Space forbids a discussion of the individual articles; suffice it to say that they all deal with the results of original work of a high order. The same careful editing notable in *Heart* under the leadership of Sir Thomas Lewis is evident in *Clinical Science,* which has retained the old format. It is to be hoped that Sir Thomas' name will continue to appear as frequently as in the past among the list of contributors; at any rate, one may be assured that a high standard of excellence will be maintained.

L'hypoglycémie. By Jean Sigwald. Price, 45 francs. Pp. 320. Paris: Gaston Doin & Cie, 1932.

The growing interest in hypoglycemia is manifested by this comprehensive monograph which contains information drawn from more than five hundred sources. Since the commonest experience with hypoglycemia has followed insulin therapy, most of the publications have appeared since 1922. The condition was noted, however, under certain circumstances long before. It is recalled that nervous symptoms accompanying depression of the blood sugar which occurred after the adminsitration of phlorhizin were described by Fischler in 1913 as "intoxicatio glykopriva." This term, or "glycopenic complex," now suggested by Sigwald, seems to be appropriate in describing the hypoglycemic syndrome; the latter term fixes attention on the change in the blood, yet the symptoms of deficiency of dextrose do not always parallel the changes in blood sugar.

The clinical signs and symptoms are discussed exhaustively, and special attention is given to the various nervous manifestations. It is pointed out that the picture may be identical although the syndrome may arise from distinctly different causes. The etiologic factors include: (*a*) hypoglycemia due to a deficiency of carbohydrate in the organism, resulting from deficient intake (extreme undernutrition or starvation), abnormal elimination (renal glycosuria, lactation) or decline in carbohydrate storage due to overexertion, damage to the liver or defects of the muscular system; (*b*) hypoglycemia due to endocrine disorders, affecting the pancreas, suprarenal glands and pituitary gland; (*c*) hypoglycemia due to nervous disorders.

Hyperinsulinism due to islet tumor of the pancreas is presented by lengthy quotation from the original report of Wilder, Allan, Power and Robertson. Other cases which have been reported by American and Canadian authors are described, and attention is directed to the success of surgical extirpation of a pancreatic tumor in relieving severe hypoglycemic symptoms, first accomplished by Howland, Campbell, Maltby and Robinson.

The clinical observations of Harris, which first suggested in 1924 the possibility of overfunction of the pancreas, are discussed, and personal observations are given by the author on a case with intense spontaneous hypoglycemia in which hyperinsulinism was suspected. Yet, in these cases in which a lesion of the pancreas has not been demonstrated by surgical operation or autopsy it is impossible to make the diagnosis of hyperinsulinism with certainty.

The book shows successfully the need for clinical recognition of hypoglycemia by thorough acquaintance with its diverse manifestations, and shows further the various factors which must be considered in determining its origin when it occurs spontaneously.

Studies from the Institute for Medical Research, Federated Malay States, Number 21. Melioidosis. By A. T. Stanton, C.M.G., M.D., F.R.C.P., and William Fletcher, M.D., M.R.C.P. Cloth. Pp. 59, with 37 illustrations. London: John Bale Sons & Danielsson, Ltd., 1932.

This book is composed of material which, for the most part, has appeared under the name of the authors at various times between 1917 and 1927. The causative organism was first described by Whitmore in 1913 and named Bacillus

pseudomallei, on account of its similarity to the organism of glanders and because the disease caused by this organism in human beings resembled human glanders. Eighty-three cases have been reported, most of which have occurred in Burma and Malaya. Only two patients have survived. The symptoms of the disease and the pathologic changes are indistinguishable from those in glanders. The organism differs from Bacillus mallei in that it is motile and usually forms a wrinkled growth on glycerin agar. The authors have described an epidemic among laboratory animals (rabbits, guinea-pigs and rats) in Kuala Lumpur probably caused by food that had been contaminated by wild rodents, which are presumably the reservoir of the infecting organism. They suggested the name Bacillus whitmori for the organism in 1921, and later (1925) pointed out that B. whitmori and certain strains of B. mallei were serologically alike.

There is no evidence of direct infection from one human being to another. Apparently infection may occur in wounds or through the gastro-intestinal tract. In fully developed cases the organisms may be cultured from the blood. The authors believe that infection is usually due to food which has been contaminated by infected rodents.

A diagnosis of melioidosis can be made only by the isolation and identification of the organism. Death usually occurs before agglutinins appear in the blood.

The illustrations show the similarity of the lesions to the lesions of glanders. Caseous nodules in the lungs, liver and spleen are common. They may occur in almost any part of the body.

B. whitmori may be differentiated from B. mallei as follows: B. whitmori is motile, B. mallei is not; B. whitmori usually gives a wrinkled growth on glycerin agar, B. mallei gives a smooth growth; B. whitmori liquefies gelatin rapidly, B. mallei either fails to liquefy gelatin or does so very slowly.

The authors believe that many more cases of melioidosis occur than are recognized, owing to the fact that there are inadequate laboratory facilities available for diagnosis.

A New Approach to Dietetic Therapy (Metabolism of Water and Minerals and Its Disturbances). By Eugene Foldes, M.D., Formerly Assistant Professor of Medicine, University of Budapest, Hungary. Cloth. Price, $5. Pp. 434. Boston: The Gorham Press, 1933.

The author of this most unusual volume attempts to show that such conditions as epilepsy, eclampsia, migraine, angina pectoris, bronchial asthma, allergic diseases, gout, essential hypertension, pernicious anemia, polycythemia, acne vulgaris, nervous and psychic disturbances, constitutional changes and aging have a common etiologic basis, namely, a disturbance in water and mineral metabolism. This disturbance may be either a generalized retention of water and salts or, as in migraine, angina pectoris and bronchial asthma, a local mobilization of fluids in the organs chiefly affected. The susceptibility of the person to such disturbances and the particular disease manifestation which results in any given case are supposed to depend on the "constitution" of the patient. The author enumerates and describes four such constitutional classes.

For all the aforementioned clinical conditions, the author advises "anti-retentional" treatment. This, as the name indicates, is designed to cause the organism to excrete its excess of water and salt. The treatment is largely dietary and consists essentially of a high protein, moderate carbohydrate, low fat diet. Water, salt and calories are moderately restricted. The use of diuretics is deprecated, but phenobarbital is recommended in those conditions in which local mobilizations are supposed to occur. Case reports are included to show the effectiveness of such treatment.

Although much of the material in this book is frankly speculative and many of the analogies drawn in support of the author's views are rather far-fetched, his hypothetic structure hangs together remarkably well. To those who have not been

exposed to the opinions contained therein, this volume offers at least some stimulating mental exercise. The very violence with which the author's ideas will be opposed by many of his readers, by initiating new thought and work, may constitute a large portion of whatever merit this book may have.

Chronic Arthritis and Fibrositis. Diagnosis and Treatment. By Bernard Langdon Wyatt, M.D. Price, $3.50. Pp. 201. New York: William Wood & Company, 1933.

This book presents in a concise manner much of the valuable information that has resulted from recent investigations in the field of arthritis. It opens with a statistical and economic statement in regard to the prevalence and importance of chronic arthritis. The second chapter presents various considerations in regard to the etiology and pathology of chronic arthritic disease. Of especial note is the effort made to evaluate the various influences of focal infection, trauma and metabolic disturbances. With a view to its bearing on subsequent therapy, the author presents detailed considerations as to differential diagnosis and renders aid in giving laboratory technic for special examinations he regards as being of value.

Approximately half of the book is devoted to therapy. The author's recommendations for diet are clear and show a desirable caution about undue enthusiasm for this method of therapy. The accepted methods of physical therapy are described and discussed in such a manner as to guide the general practitioner quite satisfactorily. The various drugs are discussed similarly. The view that chronic arthritis is a local expression of constitutional disease is clearly indicated, and the measures directed toward its allevation should support the organism as a whole.

The book is only in part a presentation of the author's experience. It constitutes a valuable summary of chronic arthritis and will be a useful guide to practitioners of general medicine and to those specializing in this field.

Traité de physiologie normale et pathologique. Tome IX. Systeme nerveux (première partie). By Roger and Binet. Price, 100 francs. Pp. 556. Paris: Masson & Cie, 1933.

This volume is part of the large system of normal and pathologic physiology by Roger and Binet designed along lines similar to those of the German work of Bethe and Bergmann. Attempts of this sort to bridge the gap between pure science and the clinic are altogether commendable, and the only criticism to be made is that the very size of the compendium precludes extensive use by the practicing physician, the man who could profit especially by it. In brief, there is danger of the compendium becoming a mausoleum.

The present volume is thoroughly done by competent men such as Binet, Cornil, Gley, Lhermitte, Nicloux, Richet and others. The initial topics are purely physiologic, such as an anatomic and physiologic description of the neuron. Matters bordering on pathology—degeneration, reflexes and tropisms—are dealt with next, followed by clinical and physiologic chapters on sensation, motility and neurologic localization. Finally come sections largely of clinical interest, such as convulsions and anesthesia. The writing is good, and one gets the impression of an adequate summary of current knowledge. Here and there is some overlapping, and unevenness can never be altogether avoided in a composite work of this sort.

Pour combattre les troubles digestifs. By Leon Schekter. Price, 15 francs. Pp. 119. Paris: Gaston Doin & Cie, 1932.

This small book is essentially a primer written for the layman. It contains a short table giving the protein, carbohydrate and fat content of common articles of diet and the components of a balanced diet. A short section is devoted to beverages and the effect of alcohol on the gastro-intestinal tract.

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